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# ARCHIVES OF DISEASE IN CHILDHOOD

INCORPORATING THE BRITISH JOURNAL OF CHILDREN'S DISEASES

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# MILK: A EUROPEAN CHILD HEALTH PROBLEM*

BY

HENRY F. HELMHOLZ

Chief Medical Consultant, United Nations International Children's Emergency Fund

It is indeed a great honour to have been invited to give the first Windermere Lecture, and it is a strange coincidence that I should have selected a topic that is so closely related to the generous donor of the Windermere Lectureship. My reason for selection of 'Milk: A European Child Health Problem' for presentation to your Association is that I think the paediatricians of Europe can play a much more important rôle in obtaining a safe pure milk supply for the children of Europe than they have in the past. Before the World War 1939-45, the milk supply of Europe was qualitatively inadequate, and the war has rendered it also quantitatively inadequate. If the present milk production can be properly developed it should result in a much improved supply, possibly an ideal supply of cows' milk for infants and children in Europe.

* The First Windermere Lecture, delivered to the British Paediatric Association at Windermere, April 16, 1948.

## The Ideal Milk Supply

Leaving out of account for the moment the fact that the ideal milk for the infant is breast milk, we can define the ideal milk supply as one that is hygienically produced, that can be delivered to the home of the consumer in a sterile condition, that will keep for a protracted period of time, in containers of a size that approximates to the immediate needs of the user, that can be converted into the appropriate feeding mixture with a minimum of effort and utensils, and that can be produced at a cost that does not preclude its use.

## European Milk Production

In table 1 is given the total milk production of European countries in 1937 and in 1946, the consumption of milk for the feeding of calves, the human consumption of liquid milk, and the amount of milk used in the manufacture of butter and cheese. There are a number of figures to which I want to call particular attention: the reduction

TABLE 1

PRODUCTION AND CONSUMPTION OF MILK IN 1,000 QUINTALS HECTOLITRE

| | Total production | | Consumption for feeding calves | | Liquid milk for human consumption | | Milk for butter, cheese, and other products | |
|---|---|---|---|---|---|---|---|---|
| | 1937 | 1946 | 1937 | 1946 | 1937 | 1946 | 1937 | 1946 |
| Austria .. .. | 23,690 | 13,540 | 3,845 | 2,770 | 11,785 | 6,100* | 8,060 | 4,700* |
| Belgium .. .. | 28,369 | 11,576 | 3,404 | 1,962 | 5,957 | 3,934 | 19,006 | — |
| Czechoslovakia .. | 46,818 | 25,546 | 3,448 | 3,032 | 25,969 | 14,893 | 17,401 | 7,621 |
| Denmark .. .. | 53,000 | 45,610 | 4,000† | 4,000† | 5,000 | 6,280‡ | 44,000 | 35,330 |
| Finland .. .. | 26,630 | — | — | — | — | — | — | — |
| France .. .. | 147,012 | 96,911 | 35,425 | 23,461 | 35,421 | 28,911 | 76,166 | 43,607 |
| Greece .. .. | 5,879 | 2,900 | — | 40 | 2,800 | 1,395 | 3,078 | 1,465 |
| Hungary .. .. | 15,260 | 7,428 | 2,988 | 1,407 | 10,350 | — | 1,922 | — |
| Ireland .. .. | 22,234 | 21,026 | 2,730 | 2,670 | 4,187 | 4,395 | 15,774 | 13,960 |
| Italy .. .. | 62,794 | 48,000 | 17,255 | 13,210 | 15,615 | 11,990 | 29,924 | 22,800 |
| Luxembourg .. | 1,454 | 1,250 | 200 | 180 | 410 | 380 | 790 | 690 |
| Netherlands .. | 53,396 | 35,814 | 1,532 | 2,200 | 14,050 | 18,665 | 37,813 | 15,593 |
| Norway .. .. | 14,050 | 12,850 | 1,000 | 1,001 | 6,090 | 7,200 | 6,960 | 4,650 |
| Poland .. .. | 100,619 | 33,782 | 8,000 | 2,800 | 52,270 | 18,700 | 40,349 | 17,325 |
| Sweden .. .. | 27,783‖ | — | — | — | — | — | — | — |
| Switzerland .. | 26,130 | 21,500 | 4,700 | 3,200 | 10,122 | 9,980 | 11,308 | 8,420 |
| United Kingdom .. | 80,960 | 83,145 | 9,590 | 6,046 | 45,550 | 66,098 | 25,502 | 10,865 |

* Estimated figure. † Including other use on farms. ‡ Including milk for cream production. ‖ Whole milk entered in dairies.

of the milk supply of Poland to one-third, from 100,619,000 hectolitres in 1937 to 33,782,000 in 1946, and the reduction to half the pre-war supply in Austria, Belgium, France, and Hungary. There is a considerable reduction in all the other countries except the United Kingdom, in which there was an increase from 80,960,000 to 83,145,000 hectolitres. Of even greater interest is the increase of

TABLE 2
PERCENTAGE OF TOTAL MILK PRODUCTION FED TO LIVESTOCK

| Countries | 1937 | 1946 |
|---|---|---|
| France .. .. .. | 24·1 | 31·0 |
| Italy .. .. .. | 22·2 | 27·5 |
| Belgium .. .. .. | 12·0 | 17·0 |
| Austria .. .. .. | 11·8 | 20·0 |
| United Kingdom .. .. | 11·0 | 7·0 |
| Poland .. .. .. | 8·0 | 9·2 |
| Denmark .. .. .. | 7·5 | 9·0 |
| Canada .. .. .. | 5·2 | 4·5 |
| U.S.A. .. .. .. | 2·6 | 4·0 |

20,548,000 hectolitres in the human consumption of liquid milk in the United Kingdom, accounted for by a 2,000,000-hectolitre increase in production, a saving of 3,500,000 in the feeding of calves, and a reduction of 14,500,000 hectolitres in the amount that went into the production of butter and cheese. Another interesting figure is the 4,500,000-hectolitre increase in the liquid milk for human consumption in the Netherlands, with a 17,500,000-hectolitre reduction in the total milk production and a 22,000,000 reduction in the milk used for butter and cheese production. A comparison of the

TABLE 3
MILK TRADE FOR THE AVERAGE YEAR BETWEEN 1934 AND 1938, IN 1,000 QUINTALS

| Country | Fresh milk | | Condensed milk | |
|---|---|---|---|---|
| | Imports | Exports | Imports | Exports |
| Austria .. .. | 1 | 57 | — | 2 |
| Belgium .. .. | 6 | 3 | 44 | 10 |
| Czechoslovakia .. | 1 | 1 | — | — |
| Denmark .. | — | — | — | 186 |
| Finland .. .. | — | 5 | — | — |
| France .. .. | — | 153 | 23 | 51 |
| Ireland .. .. | — | 26 | — | 61* |
| Italy .. .. | 3 | 17 | — | 15 |
| Netherlands .. | — | 26 | — | 1,784 |
| Norway .. .. | — | 11 | — | 21 |
| Poland .. .. | — | 2 | — | — |
| Switzerland .. | 94 | 2 | 94 | 59 |
| United Kingdom | 54 | — | 1,049 | 171* |

* Re-exports included.

percentages of milk fed to livestock in 1937 and 1946 shows (table 2) that in all the countries of Europe studied, except the United Kingdom, there was an increase in the percentage of milk fed to livestock. In 1937 the range was from 24·1 per cent. of milk fed to livestock in France to 7·5 per cent. fed in Denmark. The United Kingdom showed a decrease from 11 per cent. to 7 per cent. from 1937 to 1946. This increase, in a measure, can be explained by the increased number of female calves raised, and the resulting fact that with the reduced daily production per cow a greater percentage is needed to feed the calf. In France and Italy it is in greater measure the result of a fixed price in liquid milk and no fixed price in meat that makes it more profitable for farmers to feed the whole milk to his livestock and sell his animals as meat. In the report of the French Commission on Modernization (September, 1946) the importance of reducing the amount of milk fed to livestock is particularly stressed.

### Milk Exports and Imports

Table 3 shows the average exports and imports of the various European countries in the period from 1934 to 1938. Switzerland and the United Kingdom were the only importers of large amounts of both fresh and condensed milk, with smaller amounts imported by Belgium. France was the largest exporter of fresh milk, with Austria next and Ireland, the Netherlands, and Italy in smaller amounts. The Netherlands were by far the greatest exporters of condensed milk, followed by Denmark, England, Ireland, and Switzerland. The flow of milk was into Switzerland, the United Kingdom, and Belgium, from Denmark, Netherlands, France, and Ireland.

TABLE 4
ANNUAL MILK CONSUMPTION IN EUROPE PER PERSON, IN KILOGRAMMES, BEFORE 1939

| | | | |
|---|---|---|---|
| Switzerland .. | 290 | Germany .. .. | 125 |
| Sweden .. .. | 275 | France .. .. | 90 |
| Denmark .. .. | 260 | Hungary .. .. | 90 |
| U.S.A. .. .. | 251 | Greece .. .. | 42 |
| Holland .. .. | 150 | Italy .. .. | 30 |
| United Kingdom .. | 140 | | |

### European Milk Consumption

Table 4, giving the consumption of milk in the various countries of Europe, shows that Greece and Italy stand at the bottom of the list with 42 and 30 kg. per person per year. The consumption of milk in France and Hungary is only 90 kg. per person per year, and from that level it ranges upward to Germany with 125 kg. and Switzerland with 290 kg. per person per year. The United Kingdom rates are 140 kg. per person per year and the United States 251 kg.

### Skimmed Milk

As is to be expected, the production of skimmed milk (table 5) is highest in the two butter-producing countries, Denmark and Australia, 60 and 57 per cent. respectively, dropping down to almost one half for the Netherlands at 33 per cent. From there the range is gradually downward to the United Kingdom with only a 3 per cent. production of skimmed milk. The percentage range of the utilization of skimmed milk for human consumption is even greater. In Czechoslovakia 71 per cent. is so used, 64 per cent. in Hungary, 59 per cent. in Switzerland and Rumania, 53 per cent. in Poland, and only 4 per cent. in France and 1 per cent. in Australia. Forty-six per cent. of the 3 per cent. skimmed milk produced is used in the United Kingdom for human consumption.

I have inserted this table because it shows very well the use that is made of a very excellent supply of a cheap protein food in the various countries; and the great loss to human nutrition that there is when only 4 per cent. of it is used for human consumption, as in France. There is great need for the education of the public in the value of skimmed milk. Milk has been evaluated by the public solely on its fat content, a good milk is one that is yellow with cream and a poor milk one that is blue and thin from lack of fat. Another reason for this feeling on the part of the public no doubt is that the value of milk is determined by the Babcock test, by its fat content.

### Prices of Milk

To have available a large amount of milk for human use it is necessary that the farmer deliver his milk to the processing plants as whole milk, and not as cream, using his skimmed milk to feed to cattle, pigs, and chickens. In order that he may do this it is necessary for him to receive a better price for his whole milk than he would for the cream plus what he can make by feeding skimmed milk to his livestock and selling the stock as meat. The price that the manufacturer can pay the farmer depends on the price that he receives for the butter and the condensed or powdered skimmed milk. It is necessary that the milk be of good grade to make a fit skimmed milk powder. It is therefore necessary that a steady market be available for skimmed milk powder. As a result of the 1939-45 war the price of skimmed milk has advanced to 13 cents per lb. wholesale, but even at this price it is less than a quarter that of the whole milk powder, thus again showing that it is the fat and not the protein that is the costly part of the milk. In figuring out what a hundred dollars will buy to supply food for the greatest number of children, the W.H.O. I.C./F.A.O. Committee on Child Nutrition to advise U.N.I.C.E.F. last summer determined that skimmed milk and lard would provide protein and calcium to 30·7 persons for six months, and that skimmed milk and margarine fortified with vitamin A would give these ingredients to 20·5 people for the same time, but that dry whole milk as supplement would feed only 11·4 persons for six months. The caloric value of the mixture was practically the same. This shows the great relative value of skimmed milk as a cheap source of excellent protein for children.

### Methods of European Milk Production and Delivery

Even before the 1939-45 war the milk supply of Europe as a whole could be considered nowhere near a standard necessary for safe artificial feeding of infants. With the hygiene of milk production very poor, except on exceptional farms, with pre-cooling, rapid transportation of milk, and pasteurization plants lacking, and with most of the milk delivered in bulk rather than in bottles, there was much that could be criticized in European milk production and delivery. With the end of

TABLE 5

ESTIMATED PRODUCT OF SKIMMED MILK IN VARIOUS COUNTRIES IN 1,000 METRIC TONS

| Country | Total whole | Production skimmed | % | Utilization for food | % |
|---|---|---|---|---|---|
| U.S.A. .. .. | 56,500 | 21,000 | 37 | 5,900 | 28 |
| Canada .. .. | 7,995 | 3,225 | 40 | 217 | 7 |
| Australia .. .. | 4,990 | 2,850 | 57 | 14 | 1 |
| Denmark 1946-47 .. | 4,650 | 2,800 | 60 | 485 | 17 |
| Netherlands .. .. | 3,700 | 1,240 | 33 | 500 | 40 |
| Czechoslovakia .. | 2,730 | 860 | 31 | 590 | 71 |
| France .. .. | 10,880 | 3,100 | 28 | 124 | 4 |
| Poland .. .. | 2,790 | 750 | 27 | 400 | 53 |
| Norway .. .. | 1,140 | 250 | 22 | 60 | 24 |
| Hungary .. .. | 7,000 | 1,160 | 14 | 710 | 64 |
| Switzerland .. .. | 2,164 | 293 | 14 | 172 | 59 |
| Rumania .. .. | 2,050 | 240 | 12 | 140 | 59 |
| United Kingdom .. | 7,830 | 235 | 3 | 100 | 46 |

the war, conditions reached a low point in most countries of war-torn Europe as regards milk production. Poland was hit harder than any other country. Dr. Brockman of Gdansk told me that only 5 per cent. of milch cows remained in the province of Gdynia, and that the year before U.N.R.R.A. brought milk into Poland the infant mortality was 62 per cent. in the city of Gdynia. In Salonika it was reported that in 1941 and 1942 there was no milk, and that nutritional oedema was rampant but disappeared promptly when Swiss and Swedish shipments of milk became available. In Italy to-day nutritional oedema is still present in central and southern Italy. Dr. Fontale said he still saw a certain number of cases in his clinic, but not as frequently as formerly. The oedema in Italy he thinks is due to insufficient nutrition of the mothers who are nursing their babies and giving them only a pap of bread and water in addition to the insufficient breast milk. (I saw an eight-year-old boy giving his brother of eight months dry powdered chestnut flour in addition to mother's milk and pap of bread and water. On superficial examination the baby seemed in excellent condition.)

### U.N.R.R.A.'s Powdered Milk

It is probably safe to say that as a result of the war, the milk production in Europe was reduced roughly 50 per cent. This would have been calamitous had not U.N.R.R.A. stepped in and with its supply of powdered milk brought in an ideal food for infants and children. The powdered milk was an innovation in most homes but one that the population took to quite readily, although there was considerable opposition at first, particularly in Italy and Greece.

### Adverse Factors in Restoring the Milk Supply

The reduced milk supply of Europe is in large measure due to the destruction of from a third to one half of the milch cows of the various countries as the result of the war. There are many other factors, however, that have acted adversely in the restoration of an adequate milk production. Some of these are:

1. In the 20 per cent. to 60 per cent. of tuberculous cows the milk production is reduced as much as 50 per cent.; Bang's disease is present in from 15 to 40 per cent. among cows, and this high incidence of Bang's disease retards the growth of the herds, as the result of abortion and infertility. Trichomoniasis and persistent corpus luteum are two other causes of infertility. Mastitis, frequently of a recurring nature, reduces milk secretion progressively. Foot-and-mouth disease is endemic in many parts of Europe.
2. The relatively higher loss of milch cows of high production, and the low production per cow, as for example in Hungary from 6·1 litres per day in 1938 to 3·75 in 1946, reduced the milk available.
3. The lack of scientific care and feeding, and the lack of proper fodder, particularly of concentrated foods, such as oil cake, are responsible for the lowered amount.
4. The use of milch cows for draught purposes because of lack of horses and oxen reduced the milk supply.
5. The drought of 1947 reduced the milk production as much as 35 per cent. in some areas, and necessitated the killing (table 6) of milch cows in Czechoslovakia, Switzerland, Denmark, Holland, France, and Poland; 40,721 cows and heifers were slaughtered in September, 1946, and 59,878 cows and heifers were slaughtered in September, 1947, in Czechoslovakia.
6. The high percentage of milk fed to livestock resulted in its loss for infants and children.
7. The inadequate price paid for milk in the controlled market, only half to two-thirds that paid in the open market, or the governmental fixing of the price of milk and not of other related products, butter, cheese, and meat, had an adverse effect.

TABLE 6
EFFECT OF DROUGHT ON MILK PRODUCTION DURING THE SUMMER OF 1947: FIGURES IN THOUSAND HECTOLITRES

| Country | January | | September | |
|---|---|---|---|---|
| | 1946 | 1947 | 1946 | 1947 |
| Czechoslovakia .. | 1,867 | 1,921 | 2,258 | 1,985 |
| Denmark .. | 2,823 | 3,075 | 3,880 | 2,978 |
| Netherlands .. | 1,028 | 1,368 | 2,629 | 2,347 |
| Norway .. .. | 351 | 436 | 467 | 509 |
| Sweden .. .. | 2,600 | 2,656 | 2,984 | 2,681 |
| United Kingdom | 4,978 | 5,205 | 5,078 | 4,992 |
| American Zone of Germany .. | 2,823 | 3,075 | 3,880 | 2,978 |

### Meeting the Situation

The situation should be met by increasing the quantity and secondly by improving the quality of the milk. Many of the factors concerned improve both. The quantity of the milk can be increased by:

1. Importation of high-grade cattle.
2. Raising more female calves, sired by high-grade bulls by use of artificial insemination.
3. Teaching modern methods of care and feeding and procurement of concentrated food for milk production.
4. Vaccination of the herds to control Bang's and foot-and-mouth disease.
5. Artificial insemination with sperm of known healthy bulls to prevent trichomoniasis.
6. Dislodging manually a persistent corpus luteum.
7. Penicillin to control mastitis.
8. Testing of cows and isolating and slaughtering of known tuberculous cattle.

9. Proper sanitation, feeding, and vaccination to prevent loss of calves.
10. Reduction of milk feeding to livestock.
11. Governmental price adjustments of milk in relation to other food products, and payment of premiums to ensure milk delivery.
12. Reducing the use of milch cows for draught purposes.

The quality of the milk can be improved by:

1. Education of farm personnel, processors, and handlers in farm sanitations and hygienic milk production.
2. Pre-cooling of milk on the farm, and motor transport to processing plants in jacketed cans when needed.

TABLE 7

VARIOUS FACTORS RELATED TO MILK DISTRIBUTION IN ITALY

| Area | Population % | No. cows per sq. km. | Milk production % | Livestock feeding % | Processing facilities % |
|---|---|---|---|---|---|
| North | 46 | 488 | 80·0 | 18·2 | 73 |
| Centre | 18 | 132 | 10·6 | 43·2 | 20 |
| South | 24 | 55 | 5·6 | 30·7 | 7 |
| Islands | 11 | 50 | 3·4 | 34·0 | 1 |

3. Pasteurization of milk, packaging in bottles or other sterile containers, and constant refrigeration.
4. Production of unsweetened condensed or powdered milk.
5. Offering premiums to farmers for the production of milk with a low bacterial count.
6. Supervision of farms and milk plants by governmental milk inspectors.

When it has been determined how to increase the quantity as well as the quality of milk in Europe, what other factors are there that must concern us before making our decision as to what to recommend as the ultimate and best solution of the problem of supplying milk to infants and children ?

The following factors must be considered according to our definition of an ideal milk supply. To start with we must take a very definite stand against the use of raw milk as a food for infants and children. Even so-called certified milk has been known to contain tuberculosis bacilli and to give rise to milk-borne epidemics. Infants should not be fed bulk milk, even when pasteurized, because it is subject to frequent gross contamination and, summer or winter, is a source of danger to the infant.

We have, then, to consider on the one hand pasteurized bottled milk that is not a sterile product, that must be used within a twenty-four hour period, that can be shipped no great distance unless properly cooled; and on the other hand powdered or unsweetened condensed milk, both of which are products with excellent keeping qualities, both of which can readily be placed in the home of the user in the required weekly or monthly amounts, both of which are more difficult to use, and both of which may or may not be more expensive than pasteurized bottled milk.

TABLE 8

FRENCH DAIRY EQUIPMENT NEEDED (FRENCH COMMISSION, SEPT., 1946)

| | |
|---|---|
| Milk production | 13,500,000 |
| Pasteurization | 5,810,000 |
| Butter | 2,900,000 |
| Cheese | 1,000,000 |
| Renewal equipment | 5,000,000 |
| Total | 28,210,000 |

The following points are to be considered in arriving at a conclusion as to the relative value of the pasteurized and processed milks:

1. The complete lack of refrigeration in most European homes and in retail distribution centres.
2. The necessity of refrigerated transportation because of the unequal distribution of the milk-producing areas in the different countries. Eighty per cent. of the milk is produced in northern Italy, whereas only 46 per cent. of the population lives there (table 7).
3. The production of 75 per cent. of the milk in the so-called six-months flush period, and 25 per cent. in the slack period.
4. The cost of the equipment to produce it.
5. Disease outbreaks conveyed by milk.
6. The cost of the final milk products.

If we consider pasteurized milk versus processed milk under point one, which is the complete lack of refrigeration, there can be no question that the processed milk is a much safer product. It can be used to make up the feeding just before it is given to the infant.

Under point two, the processed milk can be shipped and stored for months without danger, as compared with a forty-eight hour limit for very good

TABLE 9

ESTIMATED COST OF EQUIPMENT FOR ADEQUATE MILK PRODUCTION IN CZECHOSLOVAKIA

| | $ |
|---|---|
| 75 Pasteurization plants | 9,000,000 |
| 8 Powdered milk plants | 3,500,000 |
| 750 Collecting centres | 12,000,000 |
| 100,000 Farm coolers | 400,000 |
| Miscellaneous cans, bottles, etc. | 2,000,000 |
| *Government Programme* 1947-1951 | |
| 50 Pasteurization plants | 6,000,000 |
| 4 Powdered milk plants | 1,750,000 |

TABLE 10

ESTIMATE OF EQUIPMENT REQUIRED TO PROCESS MILK FOR 0-1 GROUP

| Country | No. of infants in thousands | Daily requirements (thousand litres) | Yearly requirements (fluid thousand Hl.) | Yearly requirements powder (tons) | Approximate no. plants required | Approximate cost* $ |
|---|---|---|---|---|---|---|
| Czechoslovakia .. | 240 | 240 | 876 | 10,950 | 8 | 3,400,000 |
| France .. .. | 850 | 850 | 3,102 | 37,595 | 30 | 12,750,000 |
| Italy .. .. | 1,004 | 1,004 | 3,665 | 44,807 | 36 | 15,250,000 |
| Poland .. .. | 480 | 480 | 1,752 | 21,900 | 18 | 7,650,000 |

* A milk powder plant with the daily capacity of 500 hectolitres of milk will produce 6·25 tons, assuming that the plant would operate on a schedule of 200 days per year (flush period). It would produce 1,250 tons of powdered milk. The estimated cost of such a plant would be from $400,000 to $450,000.

pasteurized milk even with good refrigeration in the summer.

Under point three, the use of processed milks is the only possible way of keeping the excess milk production of the flush period for use in the slack period.

Under point four, as to the cost of plants, there is a decided advantage in the relative costs in favour of pasteurization as seen by tables 9 and 10.

Under point five, there were thirty milk-borne epidemics in the U.S.A. in 1943, twelve from pasteurized milk.

TABLE 11

COMPARATIVE PRICES OF A QUART OR A LITRE OF MILK IN FRANCE AND U.S.A.

| | Pasteurized bottled | Unsweetened condensed | Powdered |
|---|---|---|---|
| France .. | 31* | 54* | 48* |
| U.S.A. .. | 22† (43*) | 15† (32*) | 13† (29*) |

* In francs.
† In cents—official rate 214 francs to 100 cents.

Under point six, we have the figures for the three types of milk in the U.S.A. and in France, and the price here is definitely in favour of the processed milk as opposed to the bottled pasteurized product. The reverse is true in France, with the price of fluid milk fixed by the government (table 11). When we have determined that processed milk can compete with bottled pasteurized milk on the basis of cost, it becomes evident that processed milk becomes the milk of choice.

The comparative prices of a quart of pasteurized bottled, unsweetened condensed, and powdered milk (spray) in the U.S.A. and France are shown in table 12.

It remains now only to determine which of the two processed milks is the preferable one. The following considerations are of importance in making a decision:

1. Spray-dried powdered milk can be used in making up any sized feeding without waste. When a can of evaporated unsweetened milk is opened, it becomes readily contaminated if not immediately used. Powdered milk can be put up in small packages to make single feedings.

2. Europe is becoming educated to the use of powdered milk.

3. Tin is not available in adequate quantities in Europe to-day. A plastic container might solve this problem.

TABLE 12

COMPARATIVE PRICES OF VARIOUS MILKS IN U.S.A. AND IN FRANCE

| | | Pasteurized bottled | Unsweetened condensed | Powdered spray dried |
|---|---|---|---|---|
| U.S.A. .. | 1939 | 13* | 7 | 5 |
| | 1944 | 17 | 10 | 11 |
| | 1945 | 22 | 13 | 12 |
| France .. | 1947 | 26† | 54 | 48 |

* Cents. † Francs.

4. The cost of shipping of powdered milk is lower.

5. It is easier to use unsweetened condensed milk than to reconstitute powdered milk.

Of the five points considered, four are favourable to powdered milk and only the fifth is favourable to unsweetened condensed milk. Both products are valuable, but on the basis of the above consideration powdered milk seems to be the preferable one of the two processed forms.

## Summary

If by large-scale production the price differential between powdered milk and pasteurized bottled milk can be wiped out in Europe or powdered milk rendered even cheaper, as in the U.S.A. at the

present time, powdered milk should prove to be the ideal cows' milk supply for the infants and children of Europe.

The milk used locally in production areas or in communities without pasteurization facilities should be boiled before using.

All commercial fluid milk should be pasteurized, bottled, and refrigerated until used.

The use of dried skimmed milk deserves greater attention from the pediatrician for its value as a cheap protein food for children.

I want to thank the European Office of F.A.O. in Rome, and in particular Mr. M. E. Hays, Consultant on Milk to U.N.I.C.E.F., for their assistance and the use of their charts, as well as Dr. Carl Schlotthauer of the Mayo Foundation for his help in giving information on milk production as affected by disease in cattle.

# COMPLETE HEART BLOCK IN CHILDREN

## REPORT OF THREE CASES POSSIBLY ATTRIBUTABLE TO MEASLES

BY

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Heart block, congenital or acquired, is an uncommon condition in childhood; as a sequel to measles it is extremely rare. The three cases here reported are, therefore, of some interest, as in all three there is evidence of complete heart block having developed either during or shortly after an attack of measles. Furthermore, although Case 1 has since died, all three survived the immediate effects of the development of heart block.

White (1945) mentions congenital lesions, syphilis, diphtheria, rheumatism, bacterial endocarditis, and, very rarely, neoplasms, miliary tuberculosis, and trauma as causes of auriculo-ventricular block in the young. Seham (1925) in a review in Abt's 'Pediatrics' summarizes thirty-two cases of heart block in children reported up to that date. Of these cases, ten were associated with congenital lesions, nine with diphtheria, and the remainder with a variety of conditions, among them one definitely and one doubtfully associated with measles, and one with measles and influenza. Bower (1939) describes two cases in adolescents, which he attributes to measles, but the association cannot be regarded as proved, for the attack of measles had occurred in one case ten years and in the other fourteen years before the heart block was discovered; in one case there had also been a severe attack of influenza in the interval; furthermore there is no evidence that these cases were not congenital in origin. Logue and Hanson (1945) report a case of transient complete heart block in an American soldier during an attack of German measles which ran such an atypical course that the diagnosis must be regarded as doubtful. According to Leys (1943), 'partial and transient heart block is, of course, common enough in the acute infections, but, if it should become complete, the patient usually dies.' This is certainly true of diphtheria, the acute infection most commonly associated with heart block, for all reports agree that survival for any length of time after the development of complete heart block is unusual.

### Case Reports

**Case 1.** A boy, aged two years, was admitted to this hospital on Feb. 2, 1946, for the investigation of 'fits.' The first fit had occurred on Feb. 23, 1945, during an attack of measles; in the next two weeks he had about forty fits, and on March 7, 1945, he was admitted to Aberdeen City Hospital for Infectious Diseases, where physical examination showed no abnormality other than signs of bronchitis and a mild catarrhal otitis media. During his stay in hospital at this time no fits occurred; he remained afebrile and his pulse rate varied between 80 and 112. His cerebrospinal fluid was normal. On account of the pulmonary signs he was given a course of sulphadiazine. After his discharge from hospital on March 26, 1945, the fits recurred and continued at intervals; as a rule he had one to eight fits every day for a period of a week or two; then followed an interval, usually of about three weeks, during which he had no fits, and thereafter the cycle began again. The parents gave the following description of the fits: 'Sometimes there is no warning, sometimes he is fretful for a few minutes; he then gives a cry and falls down; he stops breathing and becomes blue and stiff; he remains like that for about two minutes, during which breathing starts slowly; he then becomes pale and passes off to sleep.' No clonic movements had ever been noticed but incontinence was common.

FAMILY HISTORY. The parents are alive and healthy; the patient was the fourth of five children, all healthy.

PREVIOUS HISTORY. His birth was precipitate but otherwise normal. He had always been subject to colds, but apart from the attack of measles had had no other illnesses.

PHYSICAL EXAMINATION. He was a well-developed, bright, but very nervous child. There was no cyanosis nor dyspnoea. There was muco-pus in the nasopharynx. The pulse was regular and of good volume, and its rate was 24 per minute. The apex beat was not palpable; the heart sounds were regular and pure, 24 per minute, with frequent feeble sounds audible during diastole—probably auricular beats. There was a systolic murmur at the left sternal border, loudest in the third space, conducted to the pulmonic area and for a short distance towards the apex. The blood pressure was 125/20 mm. Hg. There were rhonchi at all areas of the lungs. The liver edge was one finger's breadth below the costal margin. No other abnormality was detected.

INVESTIGATIONS. A radiograph of the chest

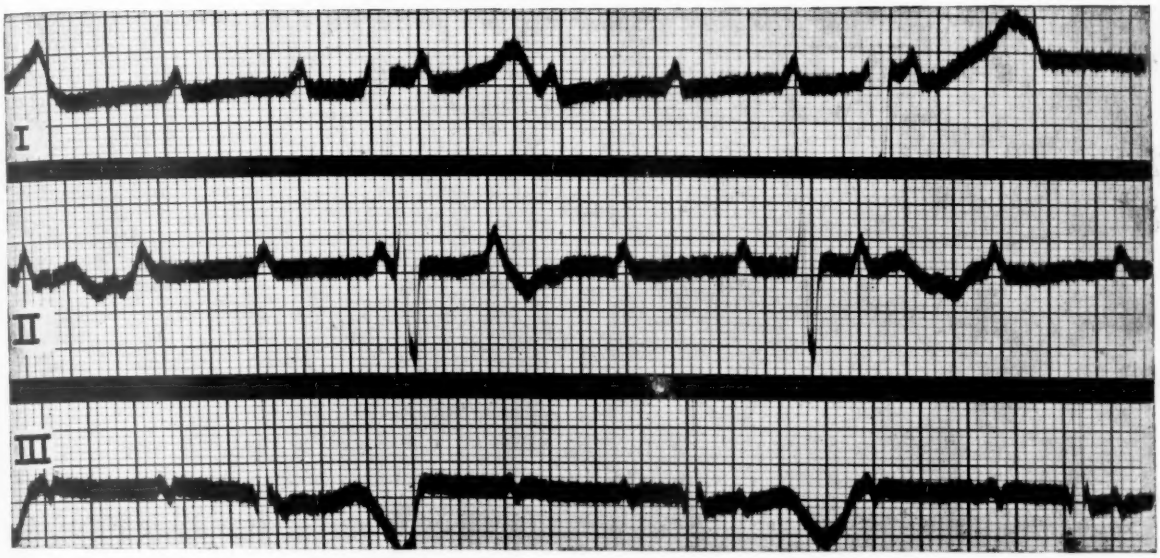


FIG. 1.—Case 1: electrocardiogram on Feb. 3, 1946.

FIG. 2.—Case 2: electrocardiogram on March 7, 1947.

PLATE I

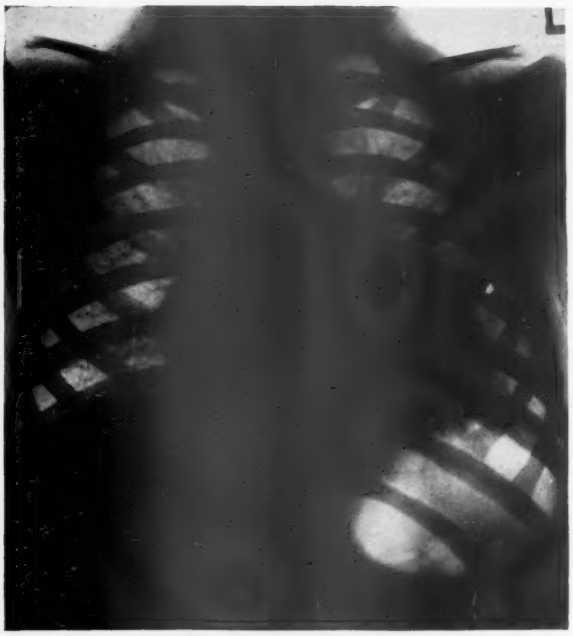


FIG. 3.—Case 2: radiograph of chest on March 10, 1947.

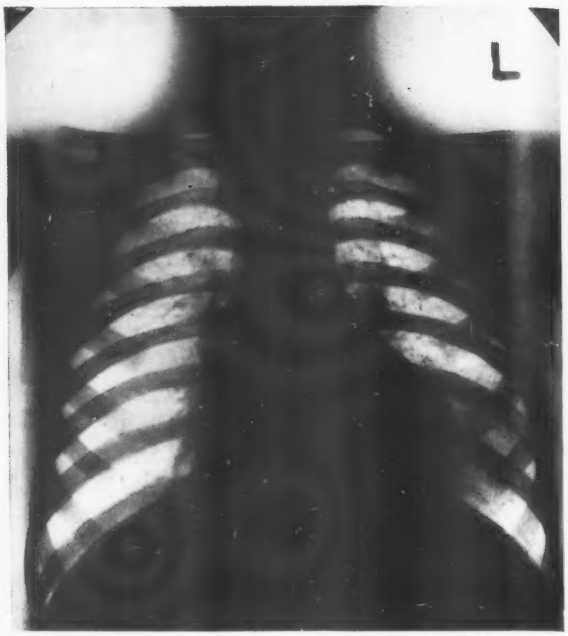


FIG. 4.—Case 3: radiograph of chest on March 20, 1947.

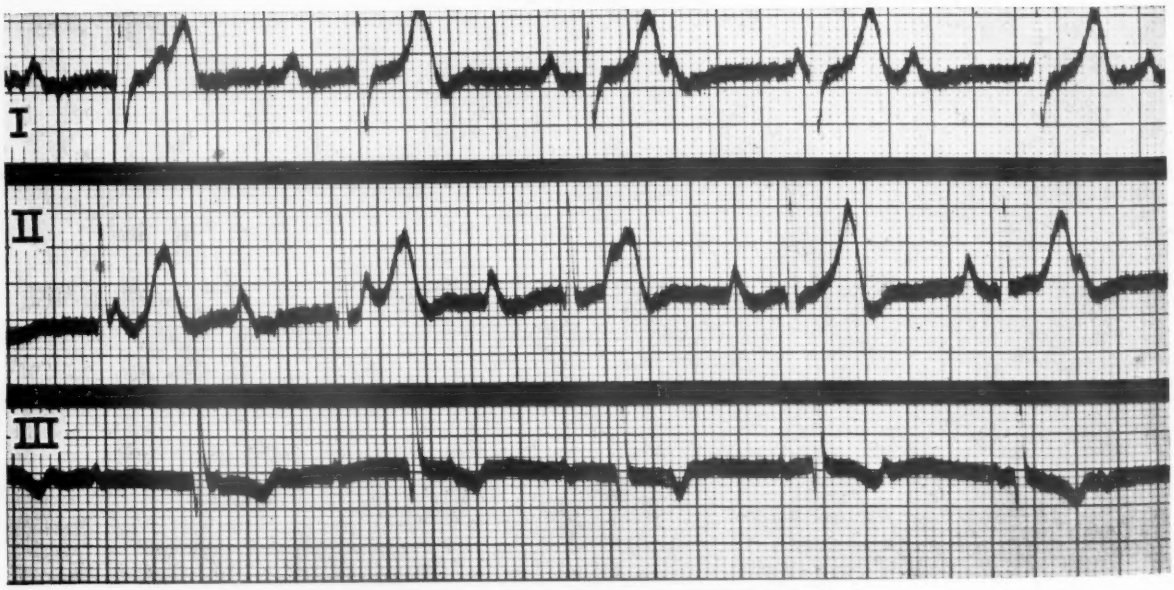


FIG. 5.—Case 3: electrocardiogram on March 26, 1947.

PLATE II

showed the heart to be globular and enlarged, probably more to the right than the left; screen examination confirmed slow, deep contractions and showed several flickering contractions on the right border between beats. An electrocardiogram (fig. 1) showed complete heart block with an auricular rate of approximately 124 and a ventricular rate of 30; right axis deviation was present. The Wassermann reaction was negative. Examination of the urine showed no abnormality. The red blood cell count was 5·6 million per c.mm. and the haemoglobin was 100 per cent. (Haldane).

During the next three weeks his condition showed no change except that the respiratory infection slowly cleared up. His pulse rate varied between 19 and 32, and in the first few days, when the bronchitis was fairly severe, was at times less than half the respiratory rate. Exercise and emotion had little effect on the heart rate, and hypodermic injections of atropine gr. 1/250 and adrenaline 0·1 ml. produced no cardiac acceleration.

On Feb. 24 he had a Stokes-Adams attack, which corresponded closely to the description of the 'fits' which he had had at home. During the next week he had similar attacks every day, the number in twenty-four hours varying from two to ten. Excitement or fear sometimes seemed to precipitate an attack, but this was inconstant and no other precipitating factor was detected. The course of a typical attack which was followed from start to finish was as follows: he gave an irritable cry and fell down; respiration became very slow and stertorous and cyanosis developed rapidly; there was urinary and faecal incontinence; no ventricular sounds were heard for thirty seconds but there were occasional fluttering sounds during this period which might have been caused by auricular beats; during the next fifty seconds six faint ventricular beats were heard but no radial pulse was palpable; normal ventricular sounds then suddenly restarted and the pulse became palpable, the rate during the next minute being sixty; with the resumption of normal ventricular beats respiration became more regular and the cyanosis faded and was succeeded by pallor; during the earlier stages of the attack he had been generally rigid, and this passed off into a state of general flaccidity without any clonic stage; he appeared conscious but dazed within two minutes of the commencement of ventricular beats; the pulse rate settled to thirty within three minutes; he remained pale and dazed for about ten minutes and thereafter appeared fairly normal but was tired and listless for the rest of the day.

After a week of daily attacks a remission occurred and there were only two isolated attacks in the succeeding twelve days. During this period he had another fairly severe attack of bronchitis and upper respiratory infection which was not accompanied by cyanosis or any evidence of cardiac embarrassment. He was discharged on March 16, 1946, his pulse rate, except during the Stokes-Adams attacks, never having risen above thirty-six throughout his stay in hospital.

On September 18, 1946, he was again seen as an out patient. Since his discharge from hospital he had continued to have attacks, at first five or six times per week, but latterly only once in about ten days. His health otherwise had been excellent; he was bright mentally and played with the other children of the family without dyspnoea or distress. On examination no change was found in his condition since his discharge from hospital; his pulse rate was 24. During examination he had a Stokes-Adams attack.

He did not report again but his condition is said to have remained unchanged until he died at home during a Stokes-Adams attack on Feb. 7, 1947.

Case 2. A girl aged five years was admitted to this hospital on Feb. 1, 1947, with the history that for the previous six months she had been listless, easily tired, and slightly breathless on exertion. For one month she had complained of some pain in the sternal region and upper abdomen, usually at night.

PREVIOUS HISTORY. At the age of six months she was admitted to Aberdeen City Hospital on account of 'marasmus.' Apart from grossly infected tonsils (which were later removed) and bilateral suppurative otitis media no abnormality was found and she was discharged after six weeks. During this time her pulse rate ranged between 110 and 130 per minute except on one occasion when a rate of 96 was recorded. She was again treated in Aberdeen City Hospital for four weeks at the age of one year and three months for infected scabies. On this occasion her pulse rate varied between 80 and 96. Apart from intermittent aural discharge and an attack of chicken pox, she had, thereafter, remained healthy until the onset of her present illness.

FAMILY HISTORY. The parents are healthy and are not consanguineous. There are five children older than the patient, all healthy, and one younger —Case 3. The parents and the five older children were examined and no cardiac abnormalities were found; all had normal electrocardiograms. The mother has had no other children, no miscarriages, and no stillbirths.

PHYSICAL EXAMINATION. She was a pale listless child with severe nasal catarrh. Her temperature was 103° F., pulse rate 100, and respiratory rate 24 per minute. The apex beat of the heart was in the fourth left interspace just beyond the nipple; there were systolic and short early diastolic murmurs at the mitral area; the systolic murmur was soft and was conducted all over the precordium; the diastolic murmur was not conducted; the pulmonary second sound was normal. There were râles at both lung bases. Examination was otherwise negative. A diagnosis of rheumatic carditis and acute bronchitis was made.

On Feb. 2 she developed a typical measles rash and on the following day she was transferred to Aberdeen City Hospital. A course of penicillin was given, and on Feb. 4 her temperature fell to

normal and remained so. Her pulse rate (see chart), which was 118 on Feb. 3, fell steadily to 90 on Feb. 6, rose again to 120 on the following morning, and remained above that level till the morning of Feb. 9. During that day she had no symptoms of any kind, but in the evening her pulse rate had fallen to 40; it remained between 40 and 60 until she was transferred back to this hospital on Feb. 18.

On examination on that date her general condition was found to have improved since her previous admission. The nasal catarrh and the râles in the lungs had cleared up. Her apex beat was now in the fifth interspace, one inch beyond the nipple line; the cardiac murmurs were unchanged. Her blood pressure was 120/90 mm. Hg, and her erythrocyte sedimentation rate was 18 mm. in one hour (Westergren).

Her waking pulse rate varied between 70 and 100, and her sleeping pulse rate between 50 and 80 per minute for the next two and a half weeks, after which the rates seldom exceeded 60 and 50 respectively.

CHART.—Case 2: pulse chart from the day following the appearance of the measles rash.

An electrocardiogram (fig. 2) on March 7 showed the presence of complete heart block with an auricular rate of 120 and a ventricular rate of 68. A radiograph of the chest on March 10 (fig. 3) showed a moderate degree of cardiac enlargement, especially to the left.

Hypodermic injections of atropine gr. 1/150 and adrenaline 0·2 ml. produced no cardiac acceleration.

She was kept at rest in bed until May 2, and was then allowed a gradually increasing amount of activity and was finally discharged on June 18, 1947. During the whole of this period she had no symptoms referable to her cardiac condition and her cardiac murmurs remained unchanged.

She was seen again as an out patient on July 12 and Nov. 11, 1947. She had remained well during this period and is said to have been as active as before her illness. On examination on both occasions no change was found in the cardiac signs. Her pulse rate remained between 40 and 50, and electrocardiograms confirmed the persistence of complete heart block.

**Case 3.** A boy aged three years, brother of Case 2, was admitted to this hospital on March 18, 1947. He had been admitted to Aberdeen City Hospital on Jan. 30, 1947, with acute bronchitis and upper respiratory infection. No cardiac abnormality was noted on admission. He was given a course of sulphamezathine and the bronchitis improved considerably. On Feb. 11, while still in the City Hospital, he developed a typical measles rash with a flare-up of the catarrhal signs in the nose and lungs. Prior to this date his pulse rate had varied between 72 and 92; thereafter, although no dramatic fall in pulse rate, such as occurred in Case 2, was observed, the pulse rate varied between 42 and 64 per minute. A radiograph on Feb. 18 was reported on as follows: 'The heart shadow is enlarged but the right border is obscured by marked congestion of the right lung, especially towards the base. The left lung is also much congested. The right heart is probably enlarged.' An electrocardiogram on March 1 showed complete heart block with an auricular rate of 96 and a ventricular rate of 65. The measles ran an otherwise uncomplicated course and he was discharged on March 2. He remained very listless, was at times breathless on exercise, and had a persistent cough until his admission to this hospital on March 18.

PREVIOUS HISTORY. He had twice been in Aberdeen City Hospital in infancy, once with bronchitis at the age of nine weeks, and once with gastro-enteritis three weeks later. He spent a total period of one month in hospital, and during this time his pulse rate was between 124 and 140 per minute. Thereafter he remained a healthy, active child.

PHYSICAL EXAMINATION. His general condition was fair; his temperature was 102° F., pulse rate 84, and respiratory rate 24 per minute. There was some nasal catarrh and a few scattered rhonchi over both lungs. The heart was not clinically enlarged; there were systolic and short mid-diastolic murmurs at the mitral area, both conducted for a short distance towards the mid-line. The blood pressure was 140/90 mm. Hg. Examination was otherwise negative.

A radiograph of the chest (fig. 4) on March 20 showed accentuated broncho-vascular markings, especially in the basal areas; the transverse cardiac diameter was slightly above the average.

An electrocardiogram on March 26 (fig. 5) showed complete heart block with an auricular rate of 110 and a ventricular rate of 60.

Hypodermic injection of adrenaline, 0·2 ml., produced no significant rise in pulse rate but there was an acceleration from 54 to 86 between thirty and fifty minutes after injection of atropine, gr. 1/150.

The signs of respiratory infection cleared up a few days after admission; the temperature fell to normal within two days and the pulse rate fell to 60 within five days. Thereafter the waking pulse rate varied between 50 and 60 and the sleeping pulse rate

between 40 and 50. The erythrocyte sedimentation rate was normal after the first week. The cardiac murmurs remained unchanged. He was kept at rest in bed until May 24 and was discharged on June 9, by which time he was moderately active. At no time did he have any symptoms referable to his cardiac condition.

He was seen as an out patient on July 12 and Nov. 11, 1947. He is stated to have remained well and active during this period, apart from a severe attack of bronchitis for which he was admitted to Aberdeen City Hospital on Oct. 2; he remained in hospital for two weeks and his bronchitis cleared up satisfactorily. On examination on July 12 and Nov. 11 the cardiac signs were unchanged except for the development of a faint systolic murmur at the pulmonary area; the second sound at this area remained normal. Electrocardiograms at both examinations confirmed the persistence of complete heart block.

## Discussion

**Etiology.** The finding of such an uncommon condition in childhood as complete heart block in a sister and brother, as in Cases 2 and 3, appears at first sight strong evidence that the condition in these cases is a familial defect. That there must have been some familial weakness in the conducting tissues of the heart appears almost certain, but this need not necessarily have been of such a degree as to produce complete heart block. The fact that both children during fairly prolonged periods in hospital in infancy had normal pulse rates is strong evidence against the heart block being congenital; cardiac rates in the region of 80 have been reported in complete block in infancy (Thomson, 1943) but, so far as I am aware, no case has been recorded with a rate over 100. Furthermore the pulse chart in Case 2 during her attack of measles can hardly be explained except on the basis of the block developing on the seventh day following the appearance of the rash; for the first four days the pulse rate fell steadily to an almost normal level; it then rose suddenly, without accompanying pyrexia, which suggests cardiac damage, and remained between 120 and 132 until the morning of the seventh day; by that evening it had dropped to 40 and it remained between 40 and 60 until the child returned to this hospital nine days later. The pulse rate in Case 3 showed no such dramatic fall, but from the day of the appearance of the measles rash it remained at a definitely lower level than previously.

Congenital heart block as a familial condition is extremely rare. Aitken (1932) quotes the case of two sisters with complete congenital heart block, originally reported by Aylward (1928), and states that this is the only authenticated example of familial block. Wallgren and Winblad (1937) subsequently reported three cases of heart block in one family. I can find no record of any other cases.

If it be accepted that the heart block in both these cases developed during the attacks of measles, then it seems certain that measles was at least a precipitating factor in the etiology.

The possibility that rheumatic carditis was also a factor in the production of the block cannot, however, be excluded in Cases 2 and 3, particularly the former, whose history prior to admission is consistent with an insidiously developing rheumatism. Case 3, however, has no such history and at the age of three is extremely young to have established rheumatic mitral disease such as would explain the murmurs heard. The possible significance of the cardiac murmurs in these two cases is further discussed under 'symptomatology.'

In Case 1 the evidence that the heart block was the result of measles is less conclusive, but the fact that the first Stokes-Adams attack occurred during the course of the measles is very suggestive of an association between the two conditions. No pulse records before the onset of measles are available in this case, but the pulse rate (80 to 112) during his admission to hospital following the first series of Stokes-Adams attacks suggests that the block at that time may have been intermittent or incomplete, which would make a diagnosis of congenital block less likely. If the block was not congenital then, presumably, it must have been due to measles, as the child had had no other illnesses.

References to cardiac lesions of any type in measles are very scanty. Griffiths and Mitchell (1941) state that 'endocarditis, pericarditis and myocarditis rarely develop.' According to Harries and Mitman (1943) the changes present in the heart are those associated with acute toxaemic conditions. It seems probable that, if the heart block in the present cases is the result of measles, it must have been caused either by an inflammatory process in the myocardium or by an ensuing fibrosis.

**Symptomatology.** Case 1 had no symptoms other than the Stokes-Adams attacks; between these attacks he was outwardly a normal child and appeared to find a cardiac rate of 20 to 30 per minute adequate for a fairly normal degree of activity. As already mentioned it is probable that the block was at first intermittent or incomplete, and the history gives no indication of the date of onset of complete and permanent block. While it is generally admitted that Stokes-Adams attacks are most likely to occur during the development of heart block, it is, as Parkinson et al. (1941) point out, a mistake to assume that, when the block becomes complete, the attacks always cease. The periodic nature of the attacks in this case remains unexplained. The attacks did not appear to be related to respiratory infection nor to any other obvious factor.

The extremely low diastolic pressure (20 mm.) in this boy can be explained adequately by the very slow cardiac rate with consequent prolonged period of diastole which would allow time for a considerable drop in pressure (Best and Taylor, 1943). There were no signs suggesting aortic incompetence.

Cases 2 and 3 have remained free from any symptoms directly referable to the heart block. This in itself is perhaps not very surprising but it does seem remarkable that neither child showed any signs of distress during the period when the block was developing; this contrasts markedly with cases of diphtheria who develop heart block, all of whom are very ill and few of whom survive.

Of physical signs in Cases 2 and 3, the most interesting and most difficult to explain are the systolic and diastolic murmurs at the mitral area, almost identical in both cases. The murmurs in site and character were indistinguishable from those heard in rheumatic mitral endocarditis and were not suggestive of any congenital lesion. In Case 2 there is a history consistent with insidiously developing rheumatic carditis, and the murmurs were certainly present before the signs of heart block appeared. It is, therefore, reasonable to argue that the original diagnosis of rheumatic carditis was correct and that it explains the cardiac murmurs. Case 3, however, is very young to have established mitral disease and has no history of any previous rheumatic manifestations. In his case the presence of the murmurs was not detected until the heart block was established, but it is possible that on his original admission to hospital with acute bronchitis the murmurs might have been obscured by the loud respiratory sounds.

The radiographs in these two cases are not inconsistent with the presence of mitral disease, and in Case 2 support is given to this diagnosis by the results of a barium swallow, which showed evidence of some enlargement of the left auricle.

**Prognosis and management.** In Case 1 the prognosis was considered poor in view of the frequency of the Stokes-Adams attacks, and this prognosis was subsequently proved correct by his death one year after first coming under observation. Alderson (1932) has reported the case of a boy, aged eleven years, with complete heart block who had had repeated Stokes-Adams attacks for three years and who remained in relatively good health though somewhat dyspnoeic on exercise. Repeated Stokes-Adams attacks are, therefore, evidently compatible with survival for some years, but it seems probable that they must in themselves damage the myocardium and materially worsen the prognosis.

The prognosis in Cases 2 and 3 is more difficult to assess. Whether the heart block is the result of localized disease in the neighbourhood of the conducting tissues or of more widespread myocarditis remains uncertain, and the possibility that both children may have rheumatic mitral disease is a further complicating factor. If the heart block is due to localized disease involving the conducting tissues, then the end result may fairly be compared to congenital block, a condition which, as Campbell (1943) has shown, is compatible not only with survival to at least early middle age but also with a comparatively active life. On the other hand, if the injury to the conducting tissues is part of a more widespread carditis, the prognosis will depend on the extent of the valvular and myocardial damage.

Both children were kept in bed for three months after the presumptive date of onset of the heart block and were thereafter allowed a gradually increasing amount of exercise. On their discharge from hospital the mother was advised not to attempt to restrict their activities provided no signs of distress appeared and the children remained otherwise healthy.

**Summary**

Three cases of complete heart block in young children are reported.

In each case it seems probable that the condition developed during an attack of measles.

One case had frequent Stokes-Adams attacks and died two years after the onset of heart block.

The other two cases, brother and sister, have had no symptoms directly referable to the heart block and are alive and well nine months after the block developed.

It is suggested that in all three cases the heart block is the result of measles, but the possibility that rheumatic carditis and some familial weakness of the conducting tissues may have played a part in the etiology of two of the cases is admitted.

I wish to express my gratitude to Professor John Craig and Dr. Ian Gordon for advice and encouragement in the preparation of this paper; to Dr. H. J. Rae for allowing me access to the records of Aberdeen City Hospital; to Dr. R. J. Duthie for the electrocardiograms; and to Dr. W. H. Milligan for the radiographs.

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# SPLENIC PANHAEMATOPENIA*

BY

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The discovery of the Rhesus factor has elucidated the nature of haemolytic disease of the newborn. In recent years several other questions have arisen in regard to the haemolytic anaemias of childhood. The old controversy of the division between a congenital and an acquired form of haemolytic jaundice has been reopened by Loutit and Mollison (1946). These authors confirmed Widal's original idea that there are two different forms of haemolytic icterus: the familial form, in which abnormal red cells are rapidly destroyed by normal lytic processes; and the acquired form, in which normal cells are rapidly destroyed by abnormal lytic processes. Lysolecithin was indicated as being the normal lytic agent. The latter conception is in accordance with the theory of Bergenheim and Fåhraeus (1936), who demonstrated that lysolecithin is formed and acts particularly in the spleen, when the blood is slowed in its passage through this reservoir.

In this connexion it is also of importance to mention a new theory, based upon experimental findings, of the cause of the physiological blood destruction after birth. Engelhardt (1947) recently demonstrated that more lysolecithin could be extracted from incubated serum or plasma of cord blood than from incubated adult serum. Owing especially to its lower cholesterol content, the serum or plasma of cord blood has less haemolysis-inhibiting effect than adult serum. In vitro, oestrone inhibits the formation of lysolecithin. The increased blood destruction which occurs after birth is due to the disappearance of oestrone during the first days of life, but this is counteracted by a rapid increase of cholesterol at this period.

## Role of the Spleen under Normal Conditions and in Haemolytic Anaemia

Apart from these investigations the role of the spleen under normal conditions and in haemolytic anaemias has been studied recently from two opposing points of view. According to one conception, participation of the spleen in physiological blood destruction can be regarded as negligible. In certain haemolytic anaemias selective splenic haemolysis is present, but is due to abnormal properties of the erythrocytes and not to primary haemolytic 'hypersplenism' (Singer, 1945). On the other hand Doan et al. (1946) hold that formation and destruction of blood elements in the normal spleen are balanced physiological functions. This equilibrium may be disturbed by a pathological dysfunction which may affect one of the cellular elements of the blood. A congenital hereditary disturbance of the physiological equilibrium may exist, or secondary dysfunction of the spleen may occur in a general constitutional disease. A combination of more than one disturbance is possible. Thus congenital and acquired haemolytic jaundice may be regarded as conditions in which destruction of the erythrocytes is an effect of disturbed splenic function. On the other hand in Werlhoff's disease the destruction of the platelets is paramount. In addition, new syndromes may be distinguished, or at least redescribed. They are: primary splenic neutropenia and primary and secondary splenic panhaematopenia.

It is known that haemolytic icterus may sometimes be combined with a moderate leukopenia, and very rarely also with a moderate thrombocytopenia, which disappear after splenectomy. In such cases the disturbed function of the spleen manifests itself primarily by increased destruction of erythrocytes. However, destruction of other blood cells may occur as a secondary phenomenon. Such cases are intermediate between simple acholuric jaundice and a condition in which all three types of circulating cellular elements of the blood are attacked, a condition called by Doan primary splenic panhaematopenia. This condition may be congenital or acquired, and in the latter case it may arise acutely or it may be secondary to pre-existing enlargement of the spleen. Proof that we are dealing with a primary dysfunction of the spleen is provided by the favourable effect of the removal of the spleen and any accessory spleens.

## Primary Splenic Panhaematopenia Distinguished from other Anaemias

Primary splenic panhaematopenia is characterized by a striking decrease in erythrocytes, leucocytes,

* Based on an address delivered at the International Congress of Physicians in London on Sept. 10, 1947.

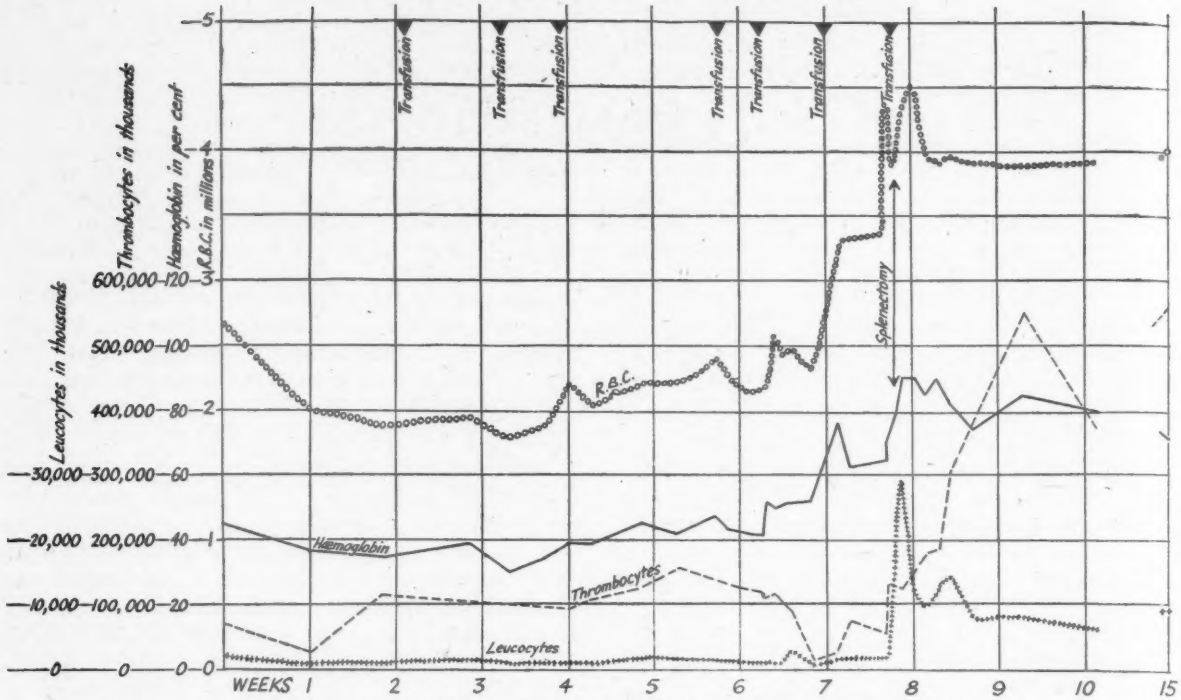


FIG. 1.—Changes in the blood before and after splenectomy in patient 1.

and platelets, but can be differentiated from aplastic or hypoplastic anaemia by the finding of hyperplastic bone marrow.

The fact that 'splenic panhaematopenia' may be secondary to splenic enlargement is of great clinical importance, but nevertheless it is not able to account for all of the extraordinary destruction of blood elements. Splenectomy does not as a rule remove the cause of the enlargement of the spleen in such cases, but it may nevertheless improve the clinical state and prolong life.

These conditions may be illustrated by a short description of two patients.

## Case Reports

### PRIMARY SPLENIC PANHAEMATOPENIA

The first case concerned a boy two years and eight months old, who entered the paediatric clinic of the University of Amsterdam with the probable diagnosis of aleukaemic leukaemia or aplastic anaemia. Following an attack of measles ten weeks before entering the hospital, the child had become very pale. He did not give the impression of being ill. The family history was unimportant. The liver was palpable one finger's breadth below the costal margin. The spleen was large and firm, and reached in the mid-line four fingers' breadth below the xiphisternum and in the anterior axillary line three fingers' breadth below the costal margin (Plate III a). The skin showed remnants of purpuric haemorrhages varying from 0·5 to 1 cm. in diameter. In the urine, urobilin was nearly always present. No blood, pigments, ova, or parasites could be found in the stools. The luetic tests of the blood serum were negative, and its content of bile pigments was not increased. There was an isochromic anaemia with marked leuco- and thrombocytopenia, and a slight decrease of the mean diameter of the erythrocytes. During the first weeks in the hospital anaemia, leucopenia, and thrombocytopenia increased; the leucocyte count fell to 1,100, the blood platelets once to as low as 14,000 per c.mm.

Three diagnostic possibilities were considered: aplastic anaemia, aleukaemic leukaemia, and so-called megaloblastic anaemia of childhood. However, puncture revealed a hyperplastic bone marrow, and all three diagnoses had to be rejected. Diseases in which splenomegaly is secondary had to be considered. Portal obstruction was regarded as improbable because there was no history of umbilical infection, there had never been a haematemesis, and no signs of varices could be found in the oesophagus. The diagnosis of Gaucher's disease was rejected, as no special indications of this disease were found in radiographs of the bones, in the skin, or in the family history.

We thought that in this boy the cause of the enlargement of the spleen lay in the organ itself or in its neighbourhood. In view of the existing haemorrhagic diathesis, splenectomy seemed justified. At operation a large spleen was found with a somewhat knobbly surface. Microscopic examination of the spleen (Plate III b and c) showed preservation of splenic architecture. The sinuses

of the pulp were much dilated and filled with a strikingly large number of cells. Among these cells were normoblasts and leucocytes, most of the latter being eosinophil. There was fibrosis of the pulp, with some increase of collagen.

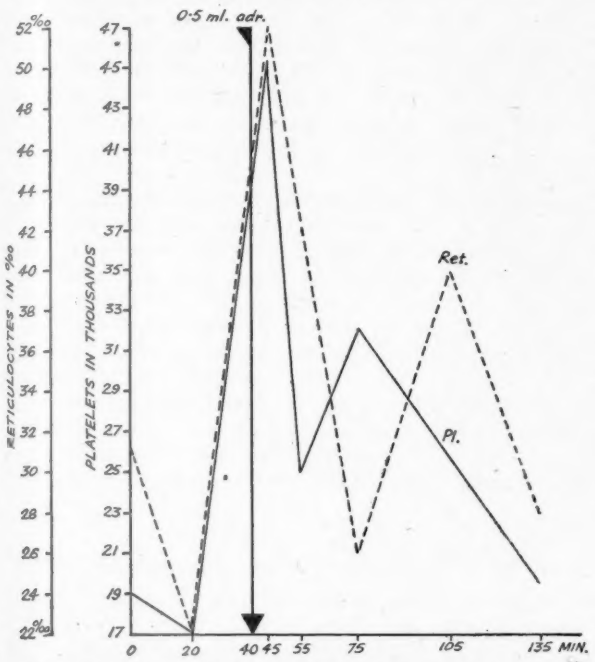


FIG. 2.—Adrenaline test (Doan) in patient 2, with secondary splenic panhaematopenia (acholuric jaundice). (Feb. 12, 1947, before operation.)

The follicles showed fibroadenosis and periarterial haemorrhages. There was also a strikingly large number of Malpighian corpuscles with proliferation of reticulo-endothelial elements and a fairly large number of neutrophils.

Biopsy of the liver did not show anything special.

The results of haematologic studies at various times after the operation are summarized in fig. 1.

At present, one year after the operation, the boy is in excellent condition.

The etiology of the splenomegaly was obscure. The deviations of the hilar vessels, established at operation, could not fully explain the enlargement. We regarded the case as an example of primary splenic panhaematopenia.

### SECONDARY SPLENIC PANHAEMATOPENIA

The girl Y. came into the paediatric clinic for the third time at the age of four and a half years. During the second admission a diagnosis of haemolytic icterus was made; the mother also suffered from chronic haemolytic anaemia. When the child was discharged from the clinic for the second time the blood, and also urine and faeces, showed all the characteristics of haemolytic jaundice, but at this time there was no leucopenia and no thrombocytopenia. The liver was felt about 3 cm., the spleen about 4 cm., below the costal margin.

At present the girl is six years old. She is a poorly developed child with yellow-brown skin. The radiograph of the wrist shows delayed skeletal development; in each wrist only two carpal bones are present. The protruding eyeballs are remarkable, and moreover there is a slightly mongoloid expression. On the skin many petechiae are present, and some purpuric spots about 1 by 2 cm. across. The abdomen is asymmetrically enlarged; the spleen occupies about the whole left part of the abdomen and protrudes (Plate IV a). The liver is palpable 4·5 cm. below the costal margin. The blood, urine, and faeces show the characteristics of haemolytic icterus with leucopenia (5,600) and marked thrombocytopenia (2,600) in addition. The icteric index is not increased.

The haemorrhagic diathesis which might be explained by the thrombocytopenia, is very unusual for (familial) haemolytic jaundice. Radiographic studies revealed widening of the marrow cavities and thinning of the cortex in tubular and flat bones (Plate IV b); the skull showed thickening without distinct striations. The changes were more or less similar to those found in Cooley's erythroblastic anaemia. The first puncture of the bone marrow, performed directly before a blood transfusion, showed few cells, and seemed to indicate a complicating hypoplastic anaemia. However, the increased number of reticulocytes was not in agreement with these findings. A second puncture, performed two weeks later, showed many blood-forming cells of the erythropoietic and of the leucopoietic system and also some megakaryocytes.

In our opinion this case could be explained as one of haemolytic anaemia, in which the extreme enlargement of the spleen had caused an increased destruction of leucocytes and thrombocytes. However, we had to collect more arguments in favour of our conception, as in hypoplastic anaemia no favourable effect can generally be expected from splenectomy. We began by giving repeated blood transfusions and in this way temporarily improved the child's condition. Then, following the method of Doan (1946), we performed an adrenaline test. After the injection of adrenaline a marked temporary increase of all cellular elements of the blood took place (figs. 2, 3, and 4). This was considered a further justification for the removal of the spleen. After some preparatory blood transfusions splenectomy was performed.

The spleen weighed 1,377 g. Microscopic examination (Dr. R. van Dam) revealed an increase in the number of follicles, some of which showed fibrous change. In some follicles there was haemorrhage round the central artery, with increase of connective tissue. The pulp showed thickening of the fibres, some of which stained red with van Gieson. The sinuses contained polynuclear neutrophils and also myelocytes; doubtful normoblasts

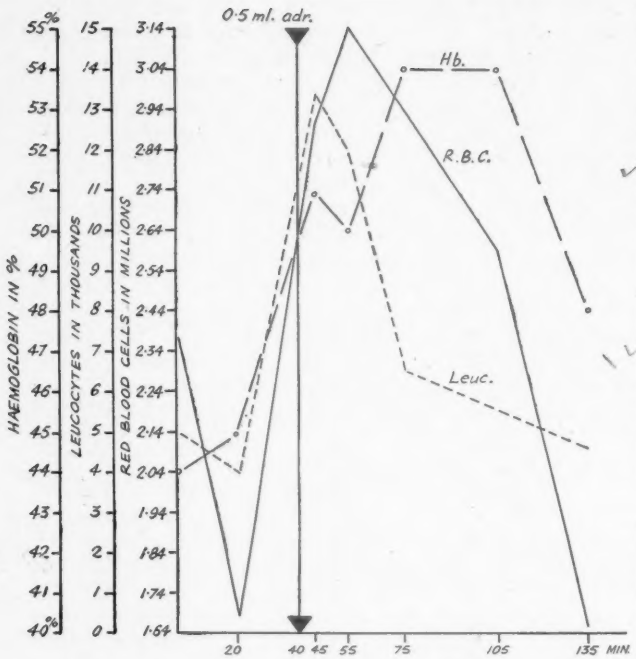


FIG. 3.—Adrenaline test (Doan) in patient 2, with secondary splenic panhaematopenia (acholuric jaundice). (Feb. 12, 1947, before operation.)

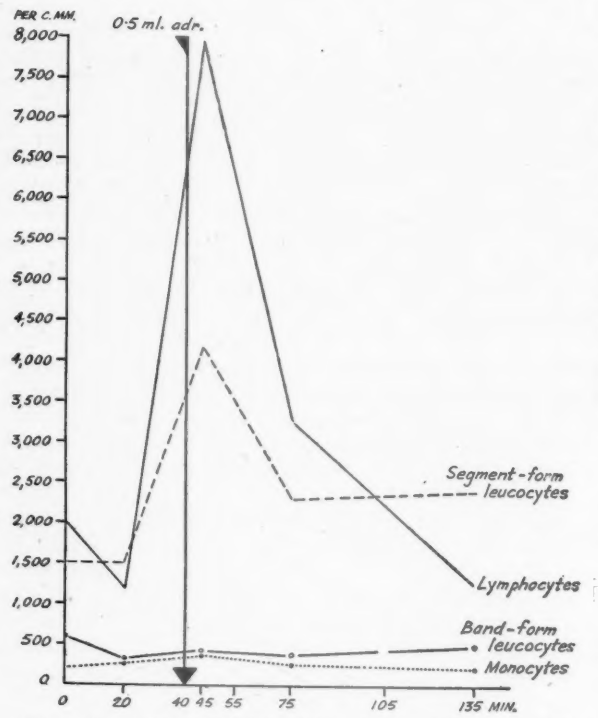


FIG. 4.—Adrenaline test (Doan) in patient 2, with secondary splenic panhaematopenia (acholuric jaundice). (Feb. 12, 1947, before operation.)

were present. A few megakaryocytes were found in the pulp. In one of the sections a Gandy-Gamma corpuscle was present (Plate IV c and d).

The girl made an uneventful recovery. Her haemoglobin, erythrocyte and leucocyte counts remained at the level obtained after the preparatory blood transfusions; the number of platelets rose immediately after the operation. The haemorrhagic diathesis disappeared, but the other characteristics of familial haemolytic jaundice are still present in the blood. The direct Coombs test was negative.

The fluctuation of the cell counts can be seen in fig. 5.

At present, five months after the operation, the girl is in perfect condition. Recently the adenoids were removed with hardly any haemorrhage. We think we are justified in presenting this girl with chronic haemolytic jaundice as an example of so-called secondary splenic panhaematopenia.

A second adrenaline test performed in this patient a few weeks ago again produced a temporary increase in the cell counts, but this increase was distinctly less pronounced than before the splenectomy (figs. 6, 7, and 8). The result of the second test corresponded to the results obtained in control tests.

## Skeletal Changes in Chronic Haemolytic Icterus

There is another point to which we want to return before concluding. The skeletal changes found in chronic haemolytic icterus, like those found in the two other chronic haemolytic anaemias (erythroblastic anaemia and sickle-cell anaemia), are secondary changes, produced by the compensatory hyperplasia of the bone marrow. It is noteworthy that our second patient showed advanced changes in the tubular bones and in the flat bones. The changes resembled those seen in erythroblastic anaemia more than usual, and were analogous to those found in a typical case of chronic haemolytic icterus (Noordenbos, 1929). The retardation in growth and development in our patient is probably partly related to the extensive skeletal changes. In none of the other cases of chronic haemolytic icterus which we have observed were the skeletal changes so intense as in our case.

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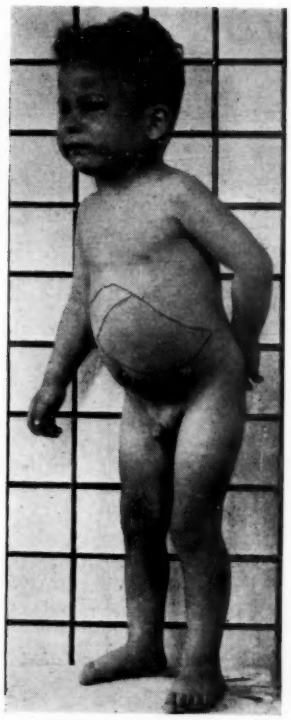
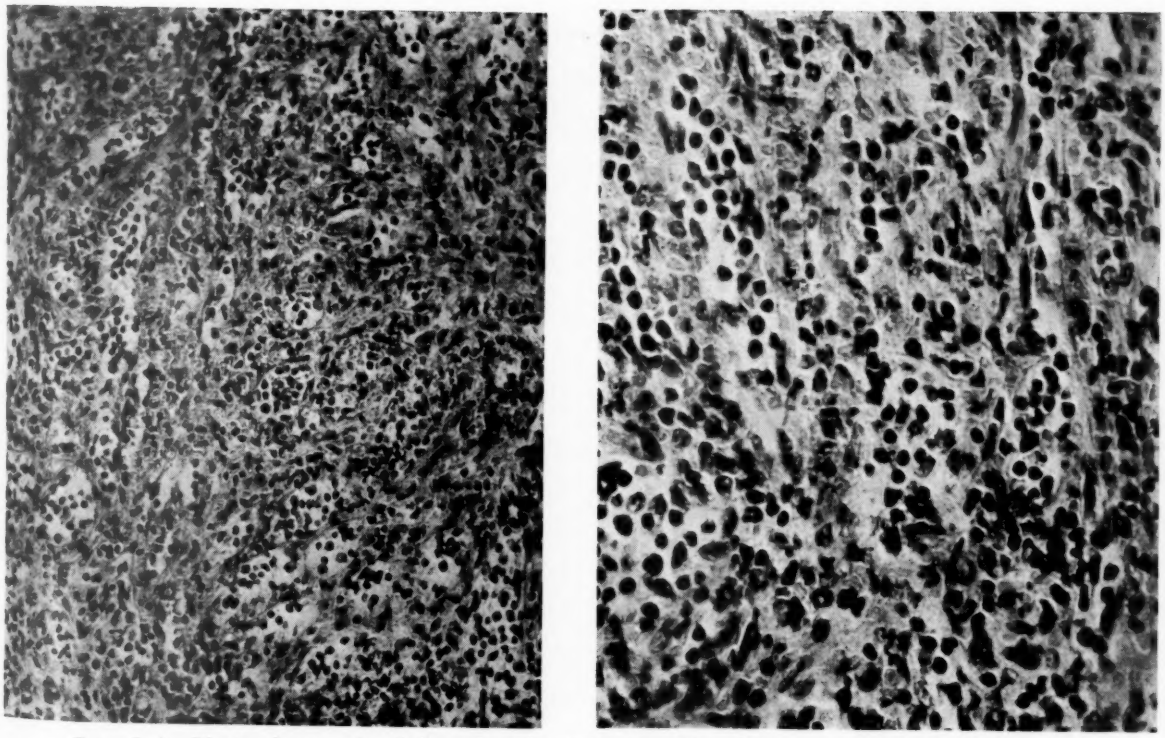


(a)—Patient 1.

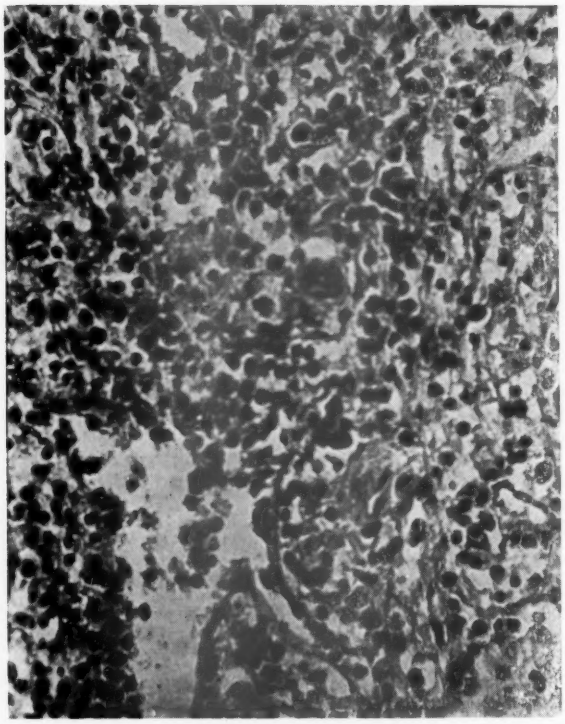


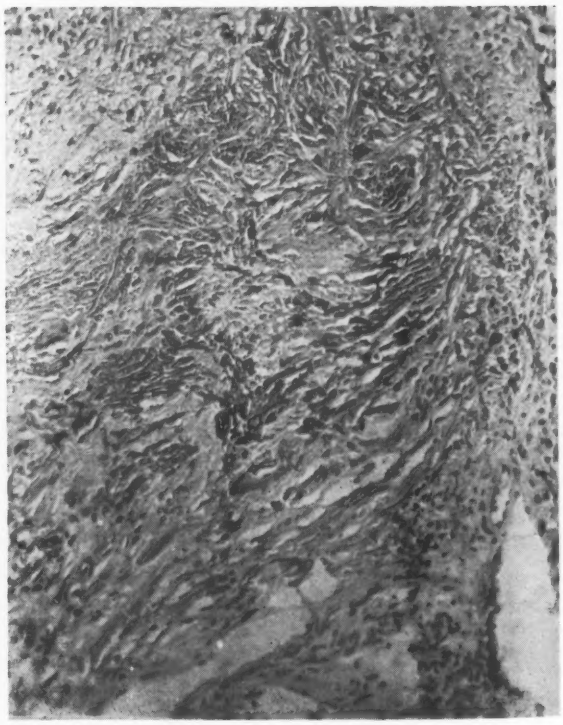
(b and c)—Photomicrograph of the spleen in patient 1 with primary splenic panhaematopenia.

PLATE III

(a)—Patient 2.

(b)—Radiograph of pelvis, patient 2.





(c and d)—Photomicrographs of the spleen in patient 2, with secondary splenic panhaematopenia.

PLATE IV

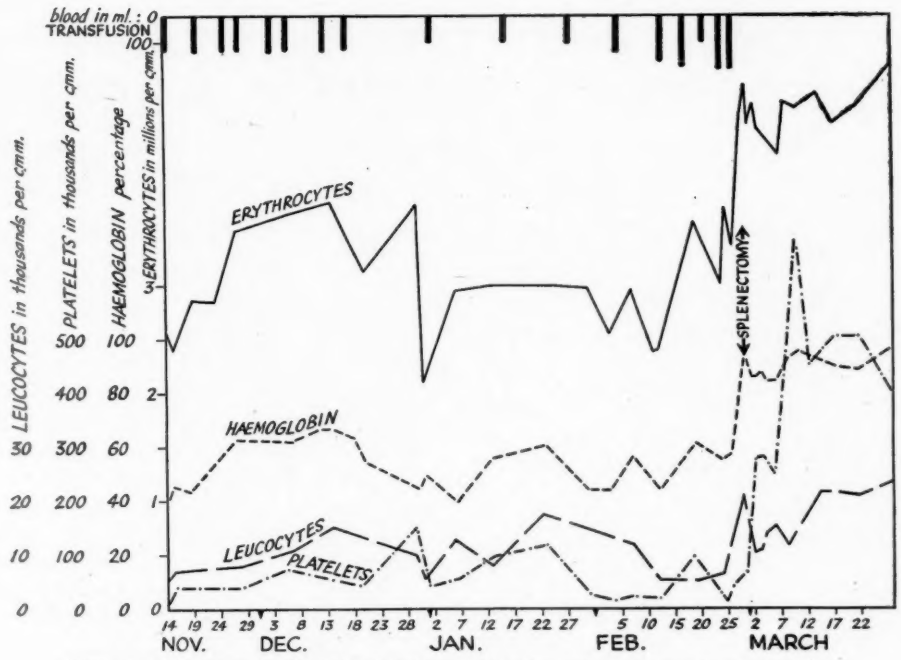



FIG. 5.—Changes in the blood before and after splenectomy in patient 2.

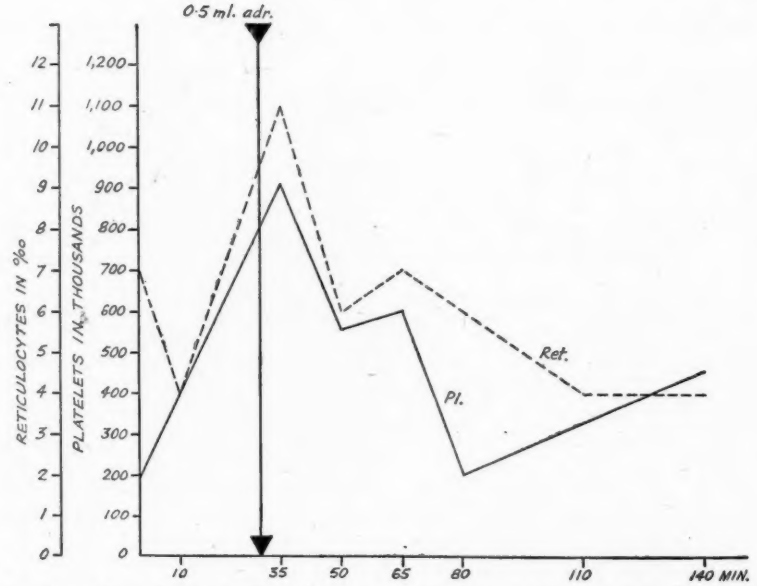



FIG. 6.—Adrenaline test (Doan) in patient 2. (Aug. 15, 1947, after operation.)

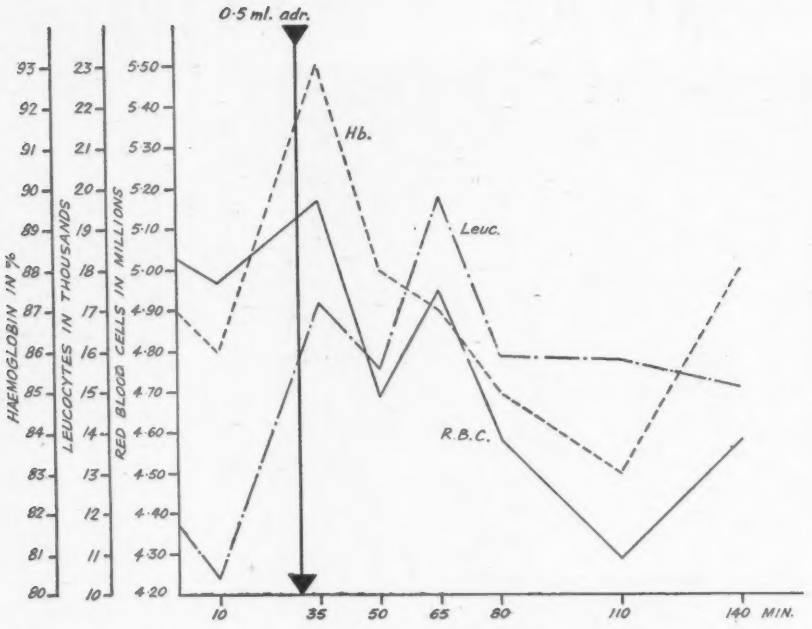



FIG. 7.—Adrenaline test (Doan) in patient 2. (Aug. 15, 1947, after operation.)

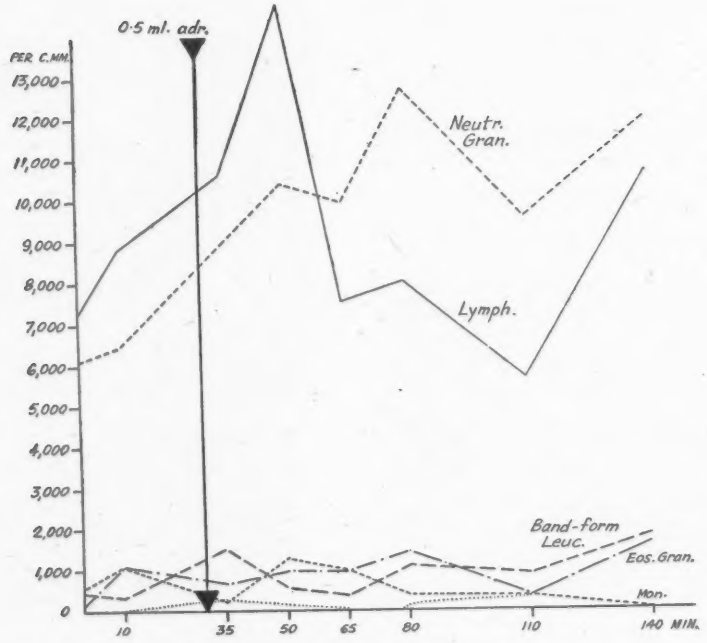



FIG. 8.—Adrenaline test (Doan) in patient 2. (Aug. 15, 1947, after operation.)

# THE NUTRITIONAL STATE OF CHILDREN WITH CHRONIC RHEUMATIC HEART DISEASE

BY

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Gray Hill (1933) stated that while the child's physical development may be arrested by severe rheumatic heart disease, most patients admitted to hospital in the active state of rheumatism or chorea are little below normal height and weight, and not uncommonly they are tall and well grown. With rest in bed the weight approached normal within a few months. The long-term effect on nutrition is by no means so clear. The problem is made more difficult because it is generally agreed that rheumatic heart disease is more common in children from poor homes (Swift, quoted from Nelson's "Loose Leaf Medicine"; Ministry of Health Report, 1927; Miller, 1928; Campbell and Warner, 1930; Glover, 1934; Medical Research Council Report, No. 114, 1927).

Vining (1928) found that 75 per cent. of his rheumatic cases were under weight as compared with fifty-nine of one hundred elementary school children with a history of good health.

### Method of Investigation

In the present investigation records of rheumatic children were available from 1927. Their numbers were few before 1932, so that only cases seen since that time have been considered. The children investigated have all attended a school cardiac clinic, where they are weighed regularly. The scales used have been tested and found accurate. The weight of each child on its last appearance at the cardiac clinic was considered to be the best criterion, because the longer the period since infection the greater the expectation of any inhibiting effect of a heart lesion on the child's growth. The ages of children when last weighed ranged between 8 and 17 years, but since the majority were between the ages of 10 and 15 years inclusive, patients outside this range were excluded. Any child with a history of serious illness other than rheumatism was not included. Thus no case having had nephritis, pulmonary tuberculosis, any long illness, or a history of erythema nodosum has been included. It is realized that a few rheumatic cases with erythema nodosum due to streptococcal sensitivity must in this way have been excluded, but it was considered a necessary precaution because of the possibility of a tuberculous etiology.

The rheumatic cases have been divided into two groups, those left with persistent signs of heart disease, and recovered cases, that is, children who have had rheumatic infection but when last seen had no evidence of heart disease. The criteria of rheumatic heart disease were the presence of one of the following: an aortic diastolic murmur, a mitral diastolic murmur, a mitral systolic murmur of organic type with or without cardiac enlargement. Mitral systolic murmurs were considered organic if loudest in the mitral area, if the murmur was louder when the child was rolled to the left and fainter when sitting upright. Any patient with a soft generalized precordial murmur was excluded even with a history of acute rheumatism, although a certain number will eventually prove to be organic. Cases of rheumatic heart disease in which the pathognomonic murmur later disappeared have not been included.

Two types of control have been used. The first consists of the recovered cases already referred to, and they were considered particularly suitable as they came from the same social class and type of home as those with organic disease, and therefore the factors of poverty and under-nutrition presumably have the same importance. The second group of controls consists of a random sample of Bristol school-children seen in 1947, there being fifty children of each sex for each year of age. They will be referred to in future as normal controls.

It is generally agreed that in the past twenty years both the height and weight of British school-children have increased greatly, so that a comparison of figures obtained in 1932 and 1947 would be invalid. The children with heart disease and the recovered cases were therefore divided into three groups (table 1). Children last weighed between 1932 and 1937 have been labelled Group A, those last weighed between 1937 and 1942 Group B, and those between 1942 and 1947 Group C. The mean weight and number of children of each year of age have been tabled, the sexes being considered separately.

Recent rheumatic infection causes a temporary loss of weight; relapses are frequent but are much more common during the first three or four years after the first attack. Thus Wilson and others (1928) found 80 per cent. of relapses occurred within three years of the first infection. Mackie (1926) found

TABLE 1

THE WEIGHT IN KILOGRAMMES OF CHILDREN WITH RHEUMATIC HEART DISEASE, OF RECOVERED CASES, AND OF NORMAL CONTROLS

| Series | Group | Sex | Type of case | Age in years | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 10 | | 11 | | 12 | | 13 | | 14 | | 15 | |
| | | | | No. | Mean wt. in kg. | No. | Mean wt. in kg. | No. | Mean wt. in kg. | No. | Mean wt. in kg. | No. | Mean wt. in kg. | No. | Mean wt. in kg. |
| I* | A | M | R.H.D. | 1 | 35·0 | 2 | 33·2 | 1 | 40·9 | 16 | 38·4 | 9 | 44·2 | 3 | 45·9 |
| | | | Recovered | Nil | — | Nil | — | 1 | 50·9 | 6 | 42·6 | 1 | 35·5 | 2 | 42·7 |
| | | F | R.H.D. | 1 | 30·0 | 2 | 36·1 | 3 | 37·7 | 18 | 43·6 | 12 | 42·1 | 1 | 39·3 |
| | | | Recovered | Nil | — | 1 | 37·7 | 1 | 28·2 | 8 | 43·1 | 7 | 44·2 | 1 | 58·2 |
| | B | M | R.H.D. | Nil | — | 2 | 39·8 | 1 | 45·5 | 8 | 39·4 | 12 | 49·0 | 2 | 46·7 |
| | | | Recovered | Nil | — | 1 | 33·6 | 2 | 33·9 | 7 | 39·3 | 5 | 53·5 | 1 | 54·1 |
| | | F | R.H.D. | Nil | — | 3 | 33·3 | 3 | 35·9 | 11 | 40·7 | 14 | 46·7 | 2 | 48·6 |
| | | | Recovered | Nil | — | 1 | 34·3 | Nil | — | 11 | 44·0 | 10 | 48·3 | 2 | 51·1 |
| | C | M | R.H.D. | 2 | 30·7 | Nil | — | 2 | 34·3 | 8 | 40·7 | 8 | 42·3 | 5 | 48·2 |
| | | | Recovered | Nil | — | 2 | 33·4 | 1 | 40·0 | 7 | 44·7 | 8 | 45·6 | 6 | 57·1 |
| | | | Normals | 50 | 31·6 | 50 | 34·7 | 50 | 37·7 | 50 | 45·1 | 50 | 50·2 | 50 | 57·2 |
| | | F | R.H.D. | Nil | — | 1 | 41·4 | 3 | 47·3 | 12 | 46·1 | 6 | 48·8 | 4 | 45·7 |
| | | | Recovered | 1 | 52·3 | Nil | — | 1 | 30·0 | 7 | 41·0 | 9 | 44·9 | 4 | 49·9 |
| | | | Normals | 50 | 31·4 | 50 | 35·4 | 50 | 40·4 | 50 | 43·5 | 50 | 50·1 | 50 | 52·8 |
| II* | A | M | R.H.D. | 2 | 33·2 | 3 | 34·4 | 1 | 40·9 | 24 | 38·4 | 16 | 43·1 | 3 | 45·9 |
| | | | Recovered | Nil | — | Nil | — | 4 | 36·6 | 9 | 41·0 | 3 | 41·8 | 2 | 43·4 |
| | | F | R.H.D. | 4 | 28·1 | 2 | 36·1 | 10 | 35·7 | 30 | 43·2 | 18 | 44·4 | 7 | 48·2 |
| | | | Recovered | 1 | 28·6 | 2 | 35·2 | 5 | 32·8 | 18 | 41·1 | 11 | 44·4 | 1 | 58·2 |
| | B | M | R.H.D. | Nil | — | 3 | 37·1 | 2 | 41·6 | 14 | 39·2 | 18 | 47·1 | 3 | 49·2 |
| | | | Recovered | 2 | 32·7 | 2 | 33·4 | 4 | 32·8 | 14 | 40·6 | 8 | 48·9 | 3 | 49·1 |
| | | F | R.H.D. | 3 | 36·5 | 7 | 33·6 | 6 | 38·7 | 24 | 43·2 | 24 | 45·9 | 4 | 51·4 |
| | | | Recovered | 1 | 33·2 | 2 | 31·7 | Nil | — | 16 | 44·9 | 19 | 50·3 | 3 | 51·1 |
| | C | M | R.H.D. | 2 | 30·7 | 2 | 30·2 | 6 | 37·0 | 10 | 43·7 | 15 | 45·0 | 6 | 49·4 |
| | | | Recovered | 1 | 43·2 | 3 | 31·5 | 1 | 40·0 | 10 | 46·4 | 13 | 46·7 | 7 | 55·0 |
| | | | Normals | 50 | 31·6 | 50 | 34·7 | 50 | 37·7 | 50 | 45·1 | 50 | 50·2 | 50 | 57·2 |
| | | F | R.H.D. | 2 | 28·2 | 5 | 37·7 | 4 | 46·6 | 14 | 45·9 | 13 | 45·6 | 5 | 46·1 |
| | | | Recovered | 3 | 37·3 | 1 | 48·2 | 3 | 36·6 | 13 | 43·1 | 20 | 48·9 | 6 | 47·1 |
| | | | Normals | 50 | 31·4 | 50 | 35·4 | 50 | 40·4 | 50 | 43·5 | 50 | 50·1 | 50 | 52·8 |

* Series I consists of cases that have had rheumatic infection at least five years before, with no recurrence during the year prior to the last weighing. Series II consists of cases that have had rheumatic infection at least two years before the last weighing, with no recurrence of infection during this two-year period.

TABLE 2
THE EFFECT OF RHEUMATIC HEART DISEASE ON NUTRITION

| Series | Group | Sex and age in years | Type of control | No. of cases with R.H.D. | No. of controls | Significant difference |
|---|---|---|---|---|---|---|
| I | A | M 12-15 | Recovered | 29 | 9 | Nil |
| | B | M 11-15 | Recovered | 25 | 16 | Nil |
| | C | M 10, 12-15 | Normal | 25 | 250 | Nil |
| | | F 11-15 | Normal | 26 | 250 | Nil |
| | ABC | M 11-15 | Recovered | 77 | 47 | 5% |
| | | F 11-15 | Recovered | 92 | 63 | Nil |
| II | A | M 12-15 | Recovered | 44 | 18 | Nil |
| | | F 10-15 | Recovered | 71 | 38 | Nil |
| | B | M 11-15 | Recovered | 40 | 31 | 5% |
| | | F 10, 11, 13-15 | Recovered | 62 | 41 | 5% |
| | C | M 10-15 | Normal | 41 | 300 | Nil |
| | | F 10-15 | Normal | 43 | 300 | Nil |
| | ABC | M 10-15 | Recovered | 125 | 84 | Nil |
| | | F 10-15 | Recovered | 176 | 125 | Nil |

57 per cent. of relapses occurred within four years of a first attack, and Kaiser (1934) found that after five years only 25 per cent. of children had recurrences. In view of these findings only those cases were considered at first who had rheumatic infection at least five years previously. There may or may not have been further attacks during the five-year period, but no case was included that had suffered from a recurrence during the twelve months prior to the last weighing. This collection of cases is referred to in future as Series I, and consists both of children with rheumatic heart disease and of recovered cases.

As the numbers in Series I were not very large a second selection to be called Series II was made. This consisted of children who have had rheumatic infection at least two years previously and no recurrence of infection during the two-year period.

All groups in this paper have been compared by an analysis of variance, and less than 5 per cent. probability that the difference could be due to chance has been considered significant.

To test the validity of the recovered cases as controls, those children in Group C, Series I, were compared with normal controls for each sex separately. No significant difference was present.

### The Effect of Long-Continued Heart Disease on Weight

In the combined Groups A, B, and C of Series I, 77 boys with rheumatic heart disease were compared with 47 recovered cases. All the patients were between the ages of 11 and 15 years, and it was found that the patients with heart disease were significantly lighter (table 2). Similarly ninety-two girls were compared with sixty-three girl controls but no significant difference was detected. Each group, save for girls in Groups B and C, was then analysed separately, and all the results showed no significant difference. Girls of Groups B and C were not compared with controls, because any difference could not be important as the combined female groups were not significantly different from the recovered controls.

Series II was treated similarly. In Group B both sexes were lighter than comparable recovered controls. Other groups showed no significant difference. When Groups A, B, and C were treated as a whole there was no significant difference.

### The Effect of Various Types of Rheumatic Disease on Growth

Jones and Bland (1935) found the prognosis as regards the heart better in chorea than rheumatic fever. Ash (1941) found that in a ten-year period after rheumatic fever 30 per cent. of children had died as compared with 16 per cent. of deaths following chorea. It seemed worth while comparing cases who had had rheumatic fever only with controls. Children in Series I only were used, as the length of follow-up would be inadequate in Series II. The numbers in Group C alone were large enough to permit analysis. No significant difference was found between such cases and normal controls (table 3).

Children with rheumatic heart disease and no previous history of rheumatic infection cannot have received the long bed rest and care which is advisable if permanent heart damage is to be avoided or minimized. It was thought that this lack of nursing might have an effect on growth. In Series I all such cases were compared with controls (table 3). The only significant difference was among Group C boys where such a difference could be found by chance in less than 1 per cent. of such groups of observations.

In Series II only members of Group B were considered because in table 2 this group alone had been significantly lighter than the controls. The results of comparison with controls of cases having

TABLE 3

THE EFFECT ON GROWTH OF RHEUMATIC FEVER ONLY, AND OF NO HISTORY OF ANY FORM OF RHEUMATIC INFECTION IN SERIES I

| Group | Sex and age | Type of infection | Type of control | No. of cases R.H.D. | No. of controls | Significant difference |
|---|---|---|---|---|---|---|
| C | M 10, 12-15 | Rheumatic fever only | Normals | 12 | 250 | Nil |
| | F 12-15 | ,, ,, | Normals | 12 | 200 | Nil |
| A | M 12-14 | No known rheumatic infection | Recovered | 7 | 7 | Nil |
| | F 12-14 | ,, ,, | Recovered | 6 | 6 | Nil |
| B | M 12-15 | ,, ,, | Recovered | 5 | 10 | Nil |
| | F 11, 13-15 | ,, ,, | Recovered | 8 | 24 | Nil |
| C | M 13-15 | ,, ,, | Normals | 9 | 150 | 1% |
| | F 11, 13-15 | ,, ,, | Normals | 9 | 200 | Nil |

had more than one attack of rheumatic infection (rheumatic fever, chorea, or both), scarlet fever only, chorea only, rheumatic fever only, or with no history of these diseases, showed no significant difference (table 4). Group B boys with a history of rheumatic fever only were not analysed as they were all heavier than the control series. The meaning of these results is doubtful because the numbers considered were small.

### The Effect of Large Hearts on Nutrition

Only cases in Series I were considered, so that a time interval of at least five years would permit cardiac disease to affect the growth of these children. Enlargement was judged clinically, and no radiographic measurements were available for confirmation, but only undoubted cases were included. All cases showed evidence of affection of the mitral, aortic, or both valves. Because the numbers were small, all groups were taken together, the sexes being considered separately. Twenty-two boys compared with forty-nine recovered controls showed no significant difference.

In the female group, where twenty-four cases were compared with sixty-one recovered controls a difference significant to 5 per cent. was found, the rheumatic children being lighter.

### Discussion

Although the number of cases analysed is quite large, only Group B in Series I were lighter than the controls. In Series II in no single group were weights significantly less than in the controls, but with all the males combined the weights were significantly lower. The significance in each case was 5 per cent., which is usually considered statistically significant in biological investigations. However, when a large number of analyses are carried out such differences would be expected 1 in 20 times even if no difference existed. The results, therefore, could be due to chance. If there is any difference, then it is small and of no practical importance.

Children with a history of rheumatic fever are very little if at all lighter than normal children. The

TABLE 4

THE EFFECT OF VARIOUS FORMS OF RHEUMATIC INFECTION ON GROWTH IN SERIES II, GROUP B

| Sex and age | Type of infection | Type of control | No. of cases with R.H.D. | No. of controls | Significant difference |
|---|---|---|---|---|---|
| M 13, 14 | Multiple* | Recovered | 6 | 22 | Nil |
| F 11-14 | Multiple* | Recovered | 8 | 37 | Nil |
| F 10, 11, 13, 14 | Scarlet fever | Recovered | 9 | 38 | Nil |
| M 13-15 | Chorea | Recovered | 7 | 25 | Nil |
| F 13-15 | Chorea | Recovered | 6 | 38 | Nil |
| F 10, 11, 13-15 | Rheumatic fever | Recovered | 30 | 41 | Nil |
| M 11-15 | No rheumatic fever, chorea, or scarlet fever | Recovered | 13 | 33 | Nil |
| F 10, 11, 13-15 | ,, ,, | Recovered | 14 | 41 | Nil |

* Multiple infection = at least two attacks of rheumatic fever, or chorea, or both.

absence of any history of rheumatic infection was significant in Group C boys only. This could be due to chance, and the suggestion is supported because although children of both sexes in Group B Series II were under weight, the type of infection showed no evidence of affecting growth.

## Conclusions

Rheumatic heart disease probably has no inhibiting effect on the growth of children once the infection has subsided. The type of rheumatic infection and the presence of cardiac enlargement are also without effect.

I wish to acknowledge my indebtedness to Professor C. Bruce Perry for his advice, encouragement, and help. Professor R. H. Parry supplied me with my normal controls, and I am very grateful to Mr. H. Todd for advice on statistics.

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# OBSERVATIONS ON THE METABOLISM OF POTASSIUM FROM A STUDY OF THE RENAL CLEARANCE

BY

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The object of the investigations recorded here was to obtain further information about the metabolism of potassium with particular reference to its rate of excretion in relation to the plasma level and to its retention, if any, by the tissues. The rôle played by potassium in the regulation of the water balance has been attracting an increasing amount of attention in recent years. It has been shown, for example, that in dehydrated infants with diarrhoea there is an excessive loss of potassium by the bowel (Butler et al., 1933). Recently, Darrow (1946) has recommended the use of a transfusion fluid for intravenous use which contains a relatively high concentration of potassium in order to replace this loss. By this means he aims at the restoration of intracellular water and salts as well as extracellular fluid. The potassium is held in the body mainly within the cells, while sodium is under normal conditions mostly without the cell—that is, in the plasma and other extracellular fluids.

Certain metabolites such as chloride are classified as threshold substances. When the concentration of such a metabolite in the blood reaches a certain level it is excreted in increasing degrees as the level rises. Such a correlation for potassium has not been found. McCance and Young (1941) estimated potassium clearances in infants and adults and noted that 'individual idiosyncrasies of which we have no certain knowledge far outweigh the influence of absolute serum levels on the clearance.' These workers showed that in adults the clearance tended to increase with the minute volume of urine secreted, while in the infants, where the urine flow was much less, this did not occur. They were unable to show any relation between the plasma level of potassium and its excretion in the urine.

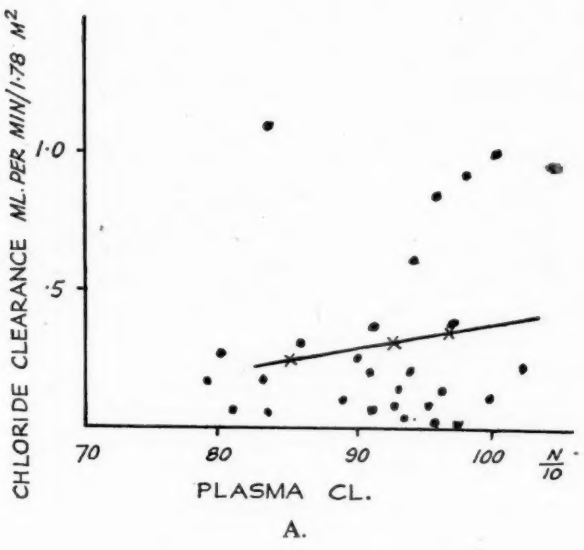
## Present Investigation

The following investigations were made in an attempt to determine the relationship between the level of potassium in the serum and its clearance by the kidney as well as its retention by the body. With one exception (a healthy adult) all the subjects were children in hospital and not suffering from any apparent acute infection or disease.

The children selected were all between seven and twelve years of age. The adult was a normal healthy male. In the case of the children a two-hours' specimen of urine was collected and venous blood drawn off in the middle of the period, one sample in oxalate under oil for plasma chloride estimation, the other clotted for serum potassium. In all, fifty potassium clearances were estimated, thirty-eight without and twelve after giving 30 grains of potassium citrate. All the investigations were carried out at least two hours after a meal. Potassium clearances are expressed as ml. per minute per square metre.

**Chemical methods.** Serum potassium was estimated by the cobaltinitrite method of Breh and Gaebler as modified by Hawk and Bergeim (1938). Where plasma potassium curves were done on the adult the micro-modification of Truszkowski and Zwemer (1937) was used. For this purpose, capillary blood was collected in heparin. Plasma chloride was estimated by Patterson's modification of the open Carius method as described by Peters and Van Slyke (1931) and fixed base by the benzidine sulphate method (Peters and Van Slyke, 1931). The potassium in urine was carried out on the phosphate-free solution used for total base estimation. Sodium in urine was calculated by the difference between fixed base and potassium. Volhard's method was used for determining chlorides in urine.

**Observations on children.** In order to show the difference in the behaviour of potassium excretion to that of chloride, observations of renal clearance in infants are graphed against the plasma levels (fig. 1a). Normally the chloride clearance tends to rise with an increase in its concentration in the plasma. In contrast, the potassium clearances (figs. 1b and c) show a different trend both before and after giving potassium citrate. The lines show that in both sets of observations, the clearance of potassium rises as the serum level falls. It will be seen that the average plasma potassium after citrate, 20·4 mg., is actually lower than without, 21·8 mg. (marked x in figs. 1a and b), although the difference, 1·4 mg., is just short of being statistically significant.



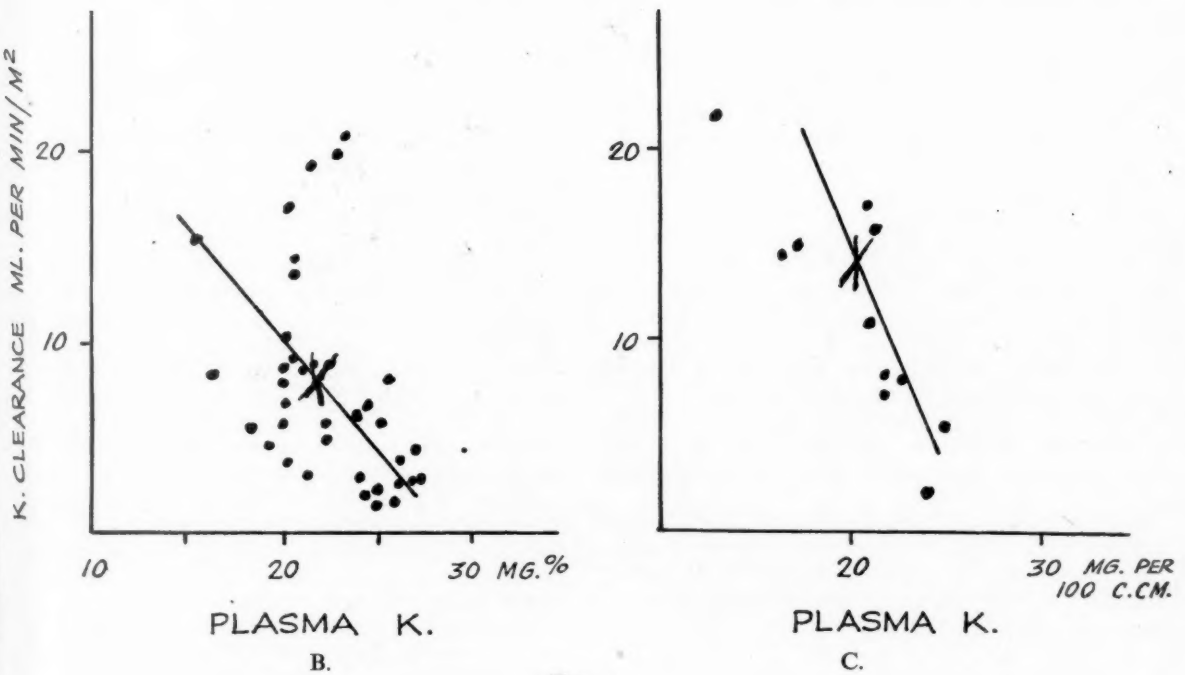
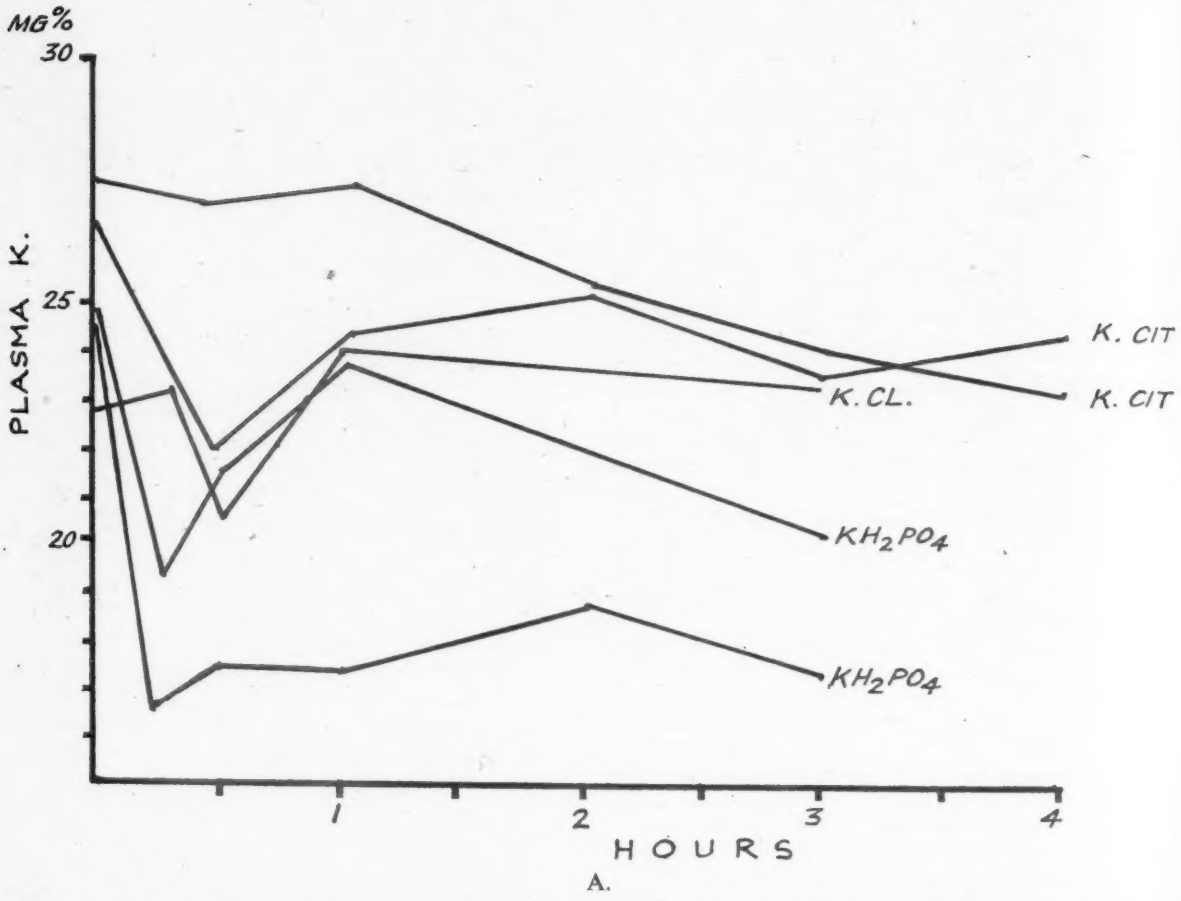




FIG. 1.

FIG. 1a.—Graph showing the relation between the plasma chloride level and the renal clearance in infants.
FIGS. 1b and c.—Graphs showing the relation between the plasma potassium level and the renal clearance in children without and after the administration of potassium citrate.




A.

FIG. 2a.—Graph showing the plasma level of potassium at intervals after the ingestion of different potassium salts

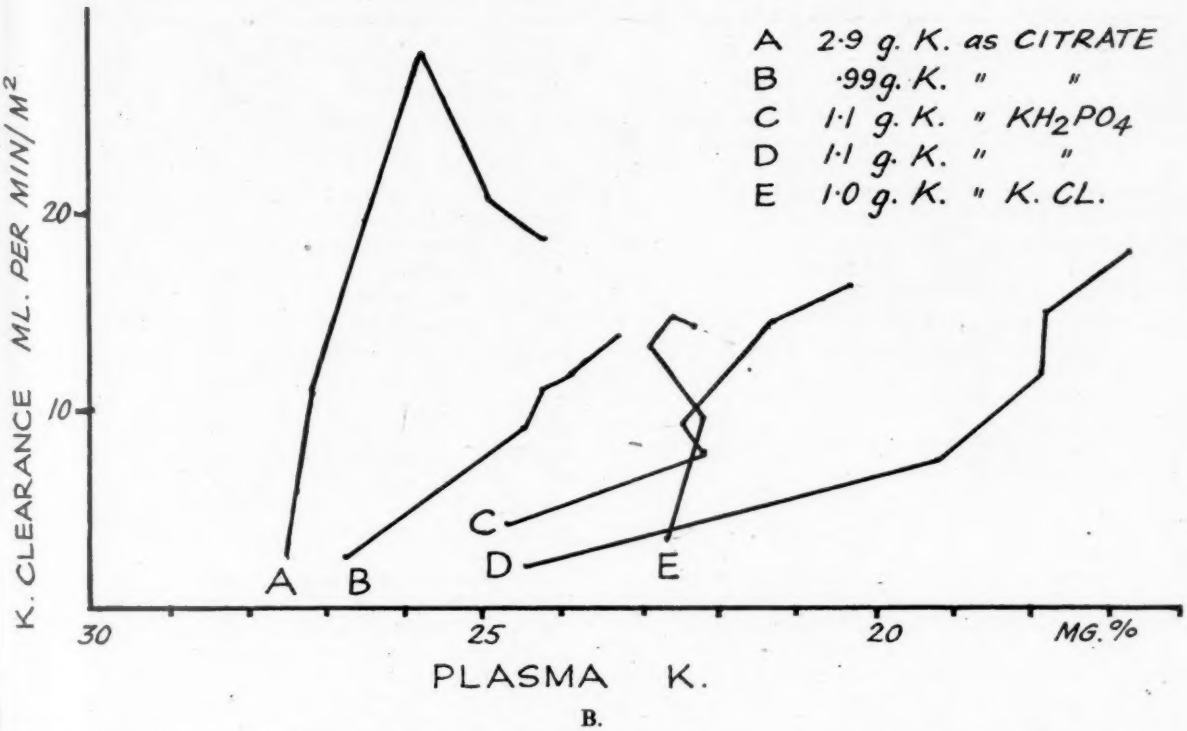
This graph indicates that potassium cannot be considered as a threshold substance in the same sense as chloride. Some factor or factors other than the plasma level is obviously involved in the excretion of potassium. If this inverse relation between plasma level and excretion is true, the corollary might be drawn that after taking a potassium salt by mouth the blood level should fall, as this ion is known to be quickly excreted. In order to test this suggestion plasma potassium curves were carried out on an adult after taking potassium salts.

**Potassium curves on plasma.** Three salts of potassium were employed, namely, the acid phosphate ($KH_2PO_4$), the chloride (KCl) and the citrate ($C_6H_8O_7K_3$), an organic salt. The amount of potassium taken as such in each case was approximately one gramme, except that on one occasion three grammes were taken as the citrate salt. No ill effects were noted. The salts were dissolved in 200 ml. water and taken by mouth.

The effect of the ingestion of potassium salts on the plasma level, the urinary output of sodium chloride, and the potassium clearance are seen in tables 1 to 5.

In calculating the potassium clearances, the figures for the plasma potassium used were the averages at the beginning and end of each hour period, except in the pre-period, when the initial figure was used, and in period I, where the values of the intervening 15- or 30-minute intervals were incorporated. The excess outputs of potassium sodium and chloride excreted in the four hours have been calculated by subtracting their excretion in the pre-period, that is, before potassium ingestion, from each succeeding hourly period and adding the total. Those figures and the plasma potassium curves are appended below each separate set of observations (tables 1 to 5).

The behaviour of the plasma potassium and its relation to the clearance are more clearly seen from the graphs (fig. 2). The plasma curve fell after giving 1 g. of potassium by mouth, except in the case of the chloride salt where the level remained almost constant. The progressive rise in the clearance accompanied by a fall in the plasma potassium




B.

FIG. 2b.—Graph showing the progressive rise in clearance and fall in plasma potassium after ingestion of potassium salts.

after the phosphate and citrate are illustrated in fig. 2b.

## Discussion

It would appear that the excretion of potassium is not determined primarily by the plasma level and that hence it cannot be considered a true threshold substance in the sense that it is excreted when the concentration in the blood rises above a certain level. Two questions must therefore be considered:

(a) What is the explanation of the fall in the plasma level after taking a potassium salt by mouth ?

(b) What determines the rate of excretion of potassium ?

The fall in the plasma level before all the ingested material has been excreted would suggest that some tissue or tissues are actively taking up the ion. Winkler and Smith (1938) showed that in dogs, after intravenous injection of potassium as the bromide, chloride, or phosphate, there was a temporary rise in the plasma potassium level. They observed also that some time after the injection had been stopped, and when a considerable amount of potassium had been excreted, the plasma level tended to rise still further. They concluded that the tissue cells had initially taken up the ion and later discharged it into the plasma. They corroborated this assumption by estimating the concentration

TABLE 1

| | | K clearance ml. per min/$m_2$ | Na output (fixed base—K) N/10 per hour | Cl output N/10 per hour |
|---|---|---|---|---|
| Pre-period | 1 hour before 1·14 g. K as $KH_2PO_4$ | 4·0 | 17·7 | 26·8 |
| Period I | 1 hour after K phosphate | 7·2 | 45·9 | 53·7 |
| Period II | 2 hours after K phosphate | 9·1 | 78·4 | 89·8 |
| Period III | 3 hours after K phosphate | 16·7 | 118·3 | 127·7 |
| Period IV | 4 hours after K phosphate | 17·1 | 90·5 | 83·0 |

Per cent. of ingested K excreted in 4 hours (145 ml. N/10) =49·5.
Excess Na excreted in 4 hours =262·3 ml. N/10.
Excess Cl excreted in 4 hours =247·1 ml. N/10.
Per cent. K retained at end of 4 hours (144 ml. N/10) =50·5.
Plasma K levels: 0 mins., 24·9; 15 mins., 19·3; 30 mins., 21·1; 1 hr., 23·6; 2 hrs., 22·1; 3 hrs., 20·3.

TABLE 2

| | | K clearance ml. per min/$m_2$ | Na output (fixed base—K) N/10 per hour | Cl output N/10 per hour |
|---|---|---|---|---|
| Pre-period | 1 hour before 1·14 g. K as $KH_2PO_4$+ 300 c. extra $H_2O$ | 2·82 | 28·8 | 30·1 |
| Period I | 1 hour after K phosphate | 7·67 | 85·3 | 94·1 |
| Period II | 2 hours after K phosphate | 12·67 | 90·7 | 134·4 |
| Period III | 3 hours after K phosphate | 14·64 | 93·3 | 151·1 |
| Period IV | 4 hours after K phosphate | 19·5 | 34·0 | 112·3 |

Per cent. of ingested K excreted in 4 hours (154·1 ml. N/10) =52·7.
Excess Na excreted in 4 hours =189·1 ml. N/10.
Excess Cl excreted in 4 hours =371·5 ml. N/10.
Per cent. K retained at end of 4 hours (138 ml. N/10) =47·3.
Plasma K levels: 0 mins., 24·6; 15 mins., 16·5; 30 mins., 17·4; 1 hr., 17·4; 2 hrs., 18·7 ; 3 hrs., 17·3.

TABLE 3

| | | K clearance ml. per min/$m_2$ | Na output (fixed base—K) N/10 per hour | Cl output N/10 per hour |
|---|---|---|---|---|
| Pre-period | 1 hour before 1·05 g. K as KCl | 3·58 | 17·58 | 21·6 |
| Period I | 1 hour after K chloride | 10·20 | 62·40 | 87·0 |
| Period II | 2 hours after K chloride | 11·60 | 70·90 | 114·2 |
| Period III | 3 hours after K chloride | 12·70 | 92·30 | 140·0 |
| Period IV | 4 hours after K chloride | 12·00 | 79·20 | 81·7 |

Per cent. of ingested K excreted in 4 hours (174 ml. N/10) =64·6.
Excess Na excreted in 4 hours =234·8 ml. N/10.
Excess Cl excreted in 4 hours =336·5 ml. N/10.
Per cent. K retained at end of 4 hours (109 ml. N/10) =35·4.
Plasma K levels: 0 mins., 22·9; 15 mins., 23·2; 30 mins., 20·4; 1 hr., 23·8; 2 hrs., 23·8; 3 hrs., 23·4.

TABLE 4

| | | K clearance ml. per min/$m_2$ | Na output (fixed base—K) N/10 per hour | Cl output N/10 per hour |
|---|---|---|---|---|
| Pre-period | 1 hour before 0·99 g. K as citrate | 2·11 | 21·5 | 24·1 |
| Period I | 1 hour after K citrate | 9·50 | 74·4 | 64·4 |
| Period II | 2 hours after K citrate | 10·10 | 100·4 | 100·7 |
| Period III | 3 hours after K citrate | 10·60 | 106·4 | 116·1 |
| Period IV | 4 hours after K citrate | 12·70 | 81·5 | 102·9 |

Per cent. of ingested K excreted in 4 hours (175 ml. N/10) =69·1.
Excess Na excreted in 4 hours =276·7 ml. N/10.
Excess Cl excreted in 4 hours =307·7 ml. N/10.
Per cent. K retained at end of 4 hours (87·7 ml. N/10) =30·1.
Plasma K levels: 0 mins., 26·9; 30 mins., 22·8; 1 hr., 24·1; 2 hrs., 25·0; 3 hrs., 23·2; 4 hrs., 24·1.

TABLE 5

| | | K clearance ml. per min/$m_2$ | Na output (fixed base—K) N/10 per hour | Cl output N/10 per hour |
|---|---|---|---|---|
| Pre-period | 1 hour before 2·96 g. K as citrate | 3·01 | 57·1 | 21·9 |
| Period I | 1 hour after K citrate | 10·90 | 106·6 | 79·8 |
| Period II | 2 hours after K citrate | 28·50 | 184·0 | 180·1 |
| Period III | 3 hours after K citrate | 20·10 | 153·0 | 148·3 |
| Period IV | 4 hours after Kcitrate | 19·80 | 158·8 | 144·9 |

Per cent. of ingested K excreted in 4 hours (459 ml. N/10) =69·1.
Excess Na excreted in 4 hours =374·0 ml. N/10.
Excess Cl excreted in 4 hours =475·5 ml. N/10.
Per cent. K retained at end of 4 hours (299·0 ml. N/10) =30·9.
Plasma K levels: 0 mins., 27·5; 30 mins., 27·2; 1 hr., 27·7; 2 hrs., 25·5; 3 hrs., 24·4; 4 hrs., 23·2.

both of potassium and of bromide in the plasma after the intravenous injection of potassium bromide. The bromide appeared to have been distributed in the extracellular fluid only, while the potassium had been more widely distributed. They concluded that after the injection of potassium salts the tissue cells take up this ion temporarily, and later discharge it into the blood. Whether potassium entered the cells by passive diffusion or by some process of active absorption could not be decided. Larson (1940) showed that after epinephrine injections the plasma potassium rises due to potassium freed from the liver. This rise is quickly followed by a fall to below the initial level. He showed that the muscles and particularly the liver were responsible for this rapid withdrawal of potassium from the blood. Stickney (1941), working with frogs, found a similar rise followed by a fall below the initial level of plasma potassium after epinephrine injections. The evidence in general appears to show that muscle and particularly liver cells readily absorb potassium from the plasma even to the extent of bringing the plasma level below the initial figure. These facts, however, would not entirely account for the fall in level and increased excretion found after oral administration. The increased clearance following oral administration might be explained on the assumption that it is not the plasma level but the degree of saturation of the liver and/or tissue cells which is the controlling factor in the excretion of potassium.

The hypothesis is therefore put forward that after oral administration the liver is quickly saturated with potassium and the kidney stimulated by some hormone or secretion to promote potassium elimination. If the rate of elimination were greater than the discharge by the liver the plasma level would fall. Cortin or one of its derivatives naturally suggests itself as the effective agent controlling the rate of excretion of potassium. In suprarenal deficiency for example, there is a retention of potassium and a rise in the plasma level. Administration of cortin leads to an increased elimination and a fall in plasma potassium. This effect of cortin is also associated with a retention of sodium chloride. In the observations recorded here, however, the increased elimination of potassium is associated with the usual increased output of sodium. This point will be discussed later.

The evidence presented so far would suggest that the excretion of potassium by the kidney is not controlled directly by the plasma level but that the concentration in the body and/or liver cells is the controlling factor. This point is worth considering when the conception of renal function tends to centre largely on its rôle as controller of the composition of the extracellular fluids. As the total potassium of the body is present mostly in the cells the mechanism proposed here would appear to be biologically useful.

Two facts emerge from this investigation:

1. The fall in the plasma level of potassium is more marked with the phosphate and scarcely noted with the chloride salt.

2. The known fact that after potassium ingestion there is an increased output of sodium and chloride in the urine.

The fall in the plasma level after the phosphate and its absence after the chloride would appear to indicate that the former is more readily taken up by the tissues than the latter, although the excess amount excreted in the four hours is approximately the same. The phosphate and the chloride differ physiologically in that the chlorine ion is an alien in the cells. It is possible that after the administration of potassium chloride the chlorine ion exerts a restraining influence on the potassium from entering the cells, and hence the fall in plasma level in the blood is not noted. The difference in the behaviour of the two salts may be of practical importance in connexion with the composition of solutions used for continuous intravenous infusion in dehydrated infants. The usual intravenous solution contains sodium chloride as the main mineral salt. As such it is suited to replace the loss of extracellular fluid and electrolyte. Butler et al. (1933) showed, however, that in gastro-enteritis there is an excess loss of potassium in the stools. This loss is more than could be accounted for by the associated breakdown of body tissue as estimated by the nitrogen output. It appeared then that in gastro-enteritis the cells were being both dehydrated and impoverished of potassium. Darrow (1946) employed fluids containing potassium chloride in concentration higher than Hartman's solution in order to replace this loss. It is suggested from the observations recorded here that possibly the phosphate rather than the chloride might prove the more effective salt for intravenous transfusion. Darrow (1946) also observed that after the transfusion had been commenced there was a potassium retention and a loss of sodium, which according to his calculations, must have come not from the extracellular fluids, but from the cells. This raises the question of the source of the excess sodium output after potassium has been taken by mouth. Two possible sources for the excess sodium may be considered, namely, the extracellular fluids and the cells. Normally the cells contain little or no sodium. Miller and Darrow (1940) showed that in rats fed on diets low in potassium the concentration of this ion fell in the muscles and was replaced up to a point by sodium. They found that approximately one millimoll of sodium replaced two millimolls of potassium. On giving potassium the sodium was eliminated. In the experiments recorded here there was a considerable excess of sodium excreted in four hours in comparison with the potassium retention at the same time. In experiments a and b (tables 1 tc 5), for instance, the excess sodium excreted in four hours was 262·3 and 189·1 millimolls respectively, while the potassium retained in the same period was 144 and 138 millimolls respectively. The excess output of sodium in

relation to potassium retained at the end of four hours is hence far above the ratio found by Miller and Darrow, namely, one millimoll of sodium displaced by two of potassium. It would appear that this excess of sodium, or at least most of it, cannot have come from within the cells. This excess sodium, moreover, is associated with a corresponding elimination of chloride—an extracellular electrolyte. Hence it can be concluded that the diuretic effect of potassium salts in the human subject is to drive out extracellular salts such as sodium chloride. The cause of this increased elimination of sodium chloride during a potassium diuresis may be due to a diminished reabsorption of salt in the renal tubules, the process of tubular reabsorption being hindered by the increased concentration of potassium ions undergoing excretion. If however, cortin is the effective agent stimulating the kidney to excrete potassium, one would expect—on an analogy with its effect in treating Addison's disease—that the sodium chloride excretion would be decreased. This question hence awaits further investigation.

## Conclusions

1. Observations on children with and without the administration of potassium citrate by mouth show that the potassium clearances tend to vary inversely with the plasma level.

2. In the adult the plasma potassium curve after potassium phosphate and citrate, but not after chloride, falls while the clearance rises. The conclusion is drawn that the main factor controlling the excretion of potassium is the saturation of the cells with this electrolyte.

3. There is evidence to show that potassium enters the cells more readily when given as the phosphate or citrate than as the chloride. The significance of this finding in relation to the composition of fluids for intravenous use in combating extracellular and intracellular dehydration is discussed.

I wish to thank Professor Stanley Graham for his help and advice in the preparation of this paper.

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# ERYTHEMA EXUDATIVUM MULTIFORME IN CHILDHOOD

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Hebra (1860) entered into a friendly rivalry with the English dermatologist Robert Willan in his classical dissertations on the ' polymorphous erythemata.' Even in these early years dermatological nomenclature had reached a complex state. Hebra comments that ' these various names by no means answer to as many distinct diseases, and our object must be to determine which of them apply merely to appearances developed in succession during the course of one and the same disease, and, in reference to this, experience has taught me that E. papulatum, E. tuberculatum, E. annulare, E. iris, E. gyratum are merely forms of the same disease according to the period of its course; to this malady I shall apply the name E. multiforme.' The phases and transitions are clearly described by Hebra and some emphasis is placed upon the regional distribution of the rash, it appearing initially on the dorsum of the hands and feet, being in severe cases more generalized even to include, in exceptional cases, the trunk and face. In Hebra's description E. papulatum represents the lowest and E. gyratum the highest grade in the eruption, and he deprecates the notion that these are different species. Also, E. exudativum multiforme may give rise to trifling subjective disorder, fever being observed only in exceptional cases and in those in which the affection spreads over large tracts of the surface and having a duration of up to four weeks. Hebra agrees with Willan that vesicular forms of the eruption may appear, but he refuses to agree that there is any relation with Herpes; and he concludes his masterly clinical description in confessing his complete ignorance of the cause of these erythemata, although his experience indicated a preponderance of these affections in young persons.

It is of some historical interest in this connexion that Hebra (1860) discusses E. epidemicum, aerodynia (which Alibert says prevailed in Paris in 1828), and classifies it as an exudative erythema. Two years later, Bazin (1862) described vesiculo-bullous stomatitis in association with multiform cutaneous lesions.

It is evident that in the following years there was much dispute in regard to the classification and etiology of the erythematous dermatoses. We now understand that individual susceptibility and reaction is indicated by a wide variation in clinical response, and this is specially so in the cutaneous and mucosal surfaces, which in their display of colour, form, shape, and distribution rarely fail to demand careful clinical scrutiny. Whilst, therefore, for certain practical reasons, many of the skin reactions arising out of general disease retain their original and historical descriptive names (which may or may not bear any clear relation to the known etiological factors in the particular case), it has not been entirely favourable in general observation in disease. Dermatological aspects have inclined to dominate description or to cause publication of cases of more general interest in relatively isolated and specialized literature. This trend in using terms according to local signs has undoubtedly led to considerable confusion, and this is specially pointed out by Levy (1947) in his observations on the ' Stevens-Johnson ' syndrome. In this, a group of signs and symptoms have received widely divergent names according to the viewpoint of the observer, or to certain variations in clinical character in individual cases. There is undoubtedly reasonable cause to gather together a group of disorders wherein particular cutaneous and mucosal responses are variably associated, and whilst the ingenuity of some of the names employed, for example dermatostomatitis, mucosal respiratory syndrome, mucocutaneous fever, etc., is recognized, none appears to be sufficiently definitive for continued use. It seems advisable to retain the name E. multiforme and to qualify the term according to additive phenomena. As Stannus (1947) points out, there are wide clinical variations in the disease, and the Stevens-Johnson syndrome belongs to or is part of the condition usually regarded as E. multiforme. Whilst Hebra in 1860 regarded E. multiforme as a primary cutaneous disease with relatively benign effects, it is clear from the literature since his day

that associated visceral pathology is not unusual and that severe illness is by no means rare. Fiessinger observed the syndrome characterized by a vesiculo-bullous eruption involving the mucous membranes, including the anal and genital regions and associated with fever and leucopenia.

Stevens and Johnson (1922) claim description of a ' new eruptive fever associated with stomatitis and ophthalmia ': the notion that it is new is probably unreal in the light of the historical facts outlined by Keil (1940) and mentioned by Levy (1947). However, no doubt Stevens and Johnson were so very impressed by the startling clinical appearances in their two cases in children that they were convinced of their unique character. In their clinical summary they note the generalized cutaneous eruption ' not conforming to any recognized dermatologic condition,' and in both cases there was a purulent conjunctivitis. In one of the boys this proceeded to panophthalmitis and total loss of vision. In the other boy severe corneal scarring resulted. A high and continuous fever was present in each case, with evidence of pulmonary involvement in one child but not so in the other. The onset was with fever, and the eruption showed identical characteristics in each, the rash appearing on the back of the neck and the chest, spreading to the face, arms, and legs during a period of about eighteen days, the last lesions to appear being on the soles and the palms at about the time when the first eruptive zones were showing resolution. The eruption showed oval dark red to purple macules which in a few days were raised firm brownish purple papules 0·5 to 2 cm. in the longest diameter, without pain or pruritus. Some foci may reveal a yellow necrotic centre. On the forearms and shins the lesions were smaller but more thickly disposed. There were no pustules. The scalp was uninvolved, but the mouth and lips were intensely sore and inflamed, and bullae appeared early on the oral mucosa. Resolution of the skin lesions was evident after three weeks, and residual faint pigmented areas, without pitting or scarring, were seen. Fall of temperature coincided with the period of resolution which finally involved the forearms and legs six weeks from the onset.

Baader (1925) observed dermato-stomatitis with pseudodiphtheritic ulceration of the lips and sublingual surface and similar scrotal erosion. Forman and Whitwell (1934) noted that herpes simplex often precedes an attack of E. multiforme. They suggest that a virus infection may be the cause of E. multiforme of the Hebra type.

Ageloff (1940) stresses the possible ocular manifestations. In his cases of E. multiforme bullosum, severe involvement of the eyes called for urgent selective treatment. In girls, vaginitis may be present. Schlesinger (1904) considered that the disease is relatively more severe in children.

We are indebted to Keil (1940) for a comprehensive historical and clinical survey of E. multiforme, wherein he notes that the variable clinical course and the complicated nomenclature has tended to create an artificial hiatus between internal medicine and dermatology. Keil regards Hebra's E. multiforme exudativum as a specific entity. The term E. multiforme is used to designate erythema-papular rashes of acute onset and brief course and having special favour for the extensor aspect of the limb, to which may be added vesicular or pustular components. The vesiculo-bullous type is more often seen by paediatricians and ophthalmologists, whilst the ordinary erythematous case runs its course with minimal subjective complaint. Involvement of mucous membranes indicates a more severe type of the disease, with correspondingly increased general effects and eruptive fever. Gross haemorrhagic bullae with widespread lesions may render it difficult to recognize the ordinary features of E. multiforme exudativum. The dangers of the disease are in proportion to the mucous membrane involvement. Superficial erosion in the mouth may be the only feature. In the eyes, secondary infection may, similarly, change the appearances. In the mouth the initial erythematous phase is quickly followed by vesicles and bullae which may extend to the palate, pharynx, larynx, tracheobronchial, and oesophageal areas, thus creating a dangerous condition. Involvement of the conjunctivae and possibly the cornea appears to follow the onset of the exanthema; pain and photophobia are succeeded by considerable swelling of the eyelids and a muco-purulent discharge. Ocular vulnerability is particularly prominent in children, the lesions varying in depth from a superficial catarrhal change to purulent reaction in which the bulbar structures may be affected. A danger exists of panophthalmitis. In the severe ocular cases there is invariably involvement of the oral and sometimes other mucosal surfaces and the cutaneous tissues. In discussing the Stevens-Johnson syndrome Keil regards it as a variant of E. multiforme exudativum with severe ocular lesions and that children are predisposed to the graver forms. Also exudative reaction may occur on the glans penis, prepuce, urinary meatus, urethra, labia, vaginal tract, cervix, anal canal, and the lower rectum; and ulcero-necrotic areas may quickly spread on the scrotum. Urethral reaction may be severe, and it is possible that some cases of non-specific urethritis are in this group. The literary term ' ectodermosis erosiva pluri-orificialis ' (Fiessinger and Rendu, 1917) represents variants of the E. multiforme exudativum syndrome in regard to the distribution of the mucous membrane lesions.

Dowling (1940) observed during 1939 six cases of a ' pemphigus-like eruption.' His description of one of the cases is specially interesting and typical of the group. ' A child of five years developed conjunctivitis followed in a few days by severe stomatitis and almost immediately afterwards small bullae appeared all over the skin. The child appeared severely though not dangerously ill, with

pyrexia. There was considerable conjunctivitis and the mouth and tongue were covered with superficial ulcers and sloughs, and the lips swollen. Blisters appeared on the penis and scrotum and similar lesions all over the surface, in largest numbers on the face and extremities. The temperature declined steadily and after eleven days' illness the child recovered.' Dowling regards E. multiforme as not a rare type of cutaneous reaction in the epidemics of winter sore throats but that the clinical severity in this particular group was unusual and the appearance of large numbers of bullae suggested pemphigus; even variola was suspected.

Raffetto and Nichols (1942) suspected that sulphadiazine was an aggravating factor in a girl aged ten years who developed, eight days after acute tonsillitis, generalized vesiculo-bullous eruptions with oral and conjunctival lesions. In this case there was 20 per cent. eosinophilia.

A similar but fatal case with oral necrosis is recorded by Dardinski (1945). Soll (1947) concludes from observations on twenty cases that sulphonamides should be avoided owing to the eruptive manifestations. Phenobarbitone is regarded by Moss and Long (1942) as a possible cause of severe toxic eruptions affecting the skin and the mucosal surfaces and closely resembling E. multiforme exudativum.

Of nearly 72,000 patients in a large infectious diseases hospital in Manhattan, twenty-eight cases of E. multiforme bullosum were recognized, all showing multiform erythematous cutaneous lesions, bullous formations in the skin and mucous membranes, and constitutional symptoms compatible with acute infectious disease. Most cases were children under ten years of age. Fever, sore throat, headache, vomiting, and anorexia, together with ocular, gastro-intestinal, respiratory, and genito-urinary symptoms were present. The principal cutaneous lesions were dark red macules and papules proceeding to vesicles and large bullae. To a less extent generalized erythema, pustules, purpura, crusted lesions, desquamation, and iritis occurred, and conjunctivitis appeared in moderate degree. There was some evidence of concurrent respiratory infection, and three cases were fatal. In this series Fletcher and Harris (1945) give special consideration to differential diagnosis. Considerable confusion was evident in the pre-admission diagnosis, haemorrhagic varicella or variola being suspected, and only one case in the whole series was correctly diagnosed before admission to hospital.

The bizarre nature of the disease is further illustrated by the studies of Stanyon and Warner (1945), who under the term ' mucosal respiratory syndrome ' describe prostrating febrile illness with mucosal involvement as conjunctivitis, membranous stomatitis, dermal eruptions, urethral lesions, and pneumonia. The initial symptoms were like influenza, with upper respiratory infection followed by lung lesions resembling the common atypical pneumonia. Bacteriological studies were essentially negative, although a virus was isolated in two cases. Of great interest is the fact that cutaneous eruption was present in only about half the cases, although there was no reason to doubt the common etiology in the series. When present, the skin lesions were very distinctive, being confined to the forearms, dorsum of hands and feet, legs, and scrotum. The stomatitis was usually an early and dominant symptom. In their fatal cases these authors found a certain distinctive pathology in the viscera and buccal mucosa but no specific infective agent could be isolated. The evidence was suggestive of a virus disease; attempts to transfer the disease to animals were unsuccessful. The Commission on Acute Respiratory Disease note also the prevalence of non-bacterial pneumonia, with essentially mononuclear reactions, in either the erythemato-papular or the vesiculo-bullous forms of E. multiforme exudativum.

In New York in 1947 (Williams) a considerable increase in the incidence of E. multiforme was seen after vaccination. In these cases there was inconspicuous oral and no conjunctival lesion. The usual interval was ten days. This phenomenon was also observed by Schwartz and Brainerd (1946) to follow five cases of smallpox vaccination, one case of tetanus toxoid injection, and in one case after injecting influenza virus vaccine. In such patients the E. multiforme response occurred at an interval of ten days. These observations lend some support to a suspected virus-allergic relationship in E. multiforme.

### Diagnosis

From the descriptive literature as first outlined by Hebra (who apparently did not record the presence of mucosal lesions) and later more elaborately discussed by a long series of observers, a picture of the bizarre manifestation of this disease may be obtained, but direct inspection of the patient is the only means of acquiring a clinical memory of the remarkable appearances usually presented. As Keil relates, the clinical pictures may be dominated by systemic disorder, varying as a rule with the intensity of the muco-cutaneous effects. Initially an upper respiratory coryzal infection or a sore throat, mild tonsillitis, pharyngitis and laryngitis, and a local lymphadenopathy may precede the exanthema by a period up to two weeks. Painful throat, dysphagia, and foetor oris may supervene. Severe coughing and possibly blood-tinged sputum may follow. The external areas of the nasal passages may be intensively irritated, and accompanied by discharge. Pyrexia may range to 105° F., and even the papular forms of the disease may be associated with considerable pyrexia. No cardiac changes have been detected. Gastro-intestinal effects are minimal, and abdominal examination is usually negative. Eosinophilia has

been recorded in a few cases, but there are usually no significant haematological findings. Haematuria may be due to erosive effects of the urethral and preputial vesicular ulceration.

Respiratory infection may arise as an extended disorder from the oral and nasal ulcero-necrotic changes or, as specially noted in the Canadian cases, primary consolidating disease in lungs may be present of a type resembling atypical pneumonia with mononuclear cell reaction.

Soll (1947) considers that cases may be divided into three groups based upon the severity and distribution of the lesions (a) as originally described by Hebra and including mild forms primarily involving the skin and showing minimal systemic disturbance or mucosal effects, (b) an extremely severe form with extensive lesions on the mucous membranes, cornea, conjunctiva, and ominous possibilities of panophthalmitis, (c) an intermediate type with most effects visible upon the mouth and other mucous membranes and a special tendency to urethritis and balanitis. Nellen (1947) relates a very characteristic example of erythema exudativum multiforme bullosum with ecchymotic conjunctivitis, stomatitis, and urethritis, and in which, after one week's illness with high fever, vesicles on an erythematous base appeared over the extensor surfaces of the arms and legs and soon the patient presented a florid picture, pus pouring from the eyes, mouth, and urethra.

The ophthalmological manifestations in E. exudativum multiforme may vary from mild hyperaemic changes to a severe pseudomembraneous form in which disastrous results may arise out of corneal ulceration. There is usually considerable swelling of the eyelids with oedema and vesicle formation, and this is well illustrated in Nellen's paper. Duke-Elder (1938) notes that Fuchs (1876) first recorded the ocular involvement, or 'herpes iris conjunctivae,' in a case which showed typical skin and oral lesions.

In a recent paper, Sneddon (1947) agrees that the eruption at the maximal phase of the disease may be generalized, but usually in the early stages the extremities, including the palms and soles, are involved, macules and papules being followed in the more severe cases by bullae. He notes that the classical target and erythema iris lesions were uncommon in his cases and that, unlike the common erythema multiforme, relapse is unusual. Subsequent attacks, however, may appear with months' or years' interval and with any or all of the previous signs, but usually with a lessened intensity. Membraneous sloughing in the mouth may be particularly severe, as in the two boys reported by Murray (1947).

### Etiology

The disease has many of the features of a primary infection. Acute upper respiratory inflammatory disorder may open up channels of entry and an interval of up to two weeks in such cases may represent an incubation period or a phase of latency in the development of cutaneous and mucosal susceptibility. The association of a virus type of pulmonary lesions in some of the cases is probably very significant and is supportive of the growing evidence in relation to virus infection in erythema exudativum multiforme. Attempts to transfer the disease to animals have so far been unsuccessful. It is significant that in their fatal cases Stanyon and Warner (1945) found in the visceral and buccal mucosa a distinct pathology suggestive of a virus disease, but no specific infective agent could be isolated. The occasional appearance of the syndrome after toxoid or vaccine injection suggests infection and allergy as operative agents. Biopsy of the skin by Nellen revealed non-specific inflammatory changes. Vesicle fluid gave negative reactions for variola and vaccinia antigens (Murray). Much of the primary pathology, especially in the mucous membranes, may be quickly changed by secondary infection, and more especially with staphylococci. Probably extended study with viruses will yield more positive information.

**Case** 1. A boy aged four years had had no previous illness. An attack of mild respiratory disorder with sore throat had begun two weeks previous to the appearance of 'spots on the legs,' which were shortly followed by a similar eruption on the legs, face, chest, and back. The wrists became painful. In another twenty-four hours the rash became haemorrhagic. The mouth was sore, reddened, and very oedematous, and there was some blood-stained mucous in the throat. The clinical picture on admission to hospital was somewhat startling and clearly indicated an unusual disorder. The boy had a pallid, puffy face with considerable oedema; suffusion and haemorrhagic eruptions were present in and around the conjunctivae. The mouth and lips were very swollen, intensely sore, and discharging haemorrhagic secretions. The tonsils and pharynx were hyperaemic. On the face, arms, feet, buttocks, and thighs a haemorrhagic papulo-bullous eruption was present, the maximum distribution of the rash being rather peripheral and chiefly on the extensor aspects. There was pain and swelling of the joints, especially the knees and wrists, and moderate effusion appeared in the left knee. There were no abnormal cardiac or pulmonary signs, and the nervous system was normal. The spleen was not enlarged, and abdominal examination was negative. Blood examination showed no abnormality apart from a slight neutrophil leucocytosis. There was no eosinophilia.

FIG. 1.

FIG. 2.

FIGS. 1 and 2.—Maximum phase of the eruption, Case 1.

FIG. 3.

FIG. 4.

FIGS. 3 and 4.—Maximum phase of the eruption, Case 2. Note confluence and vesicular formation on the face and forehead.

PLATE V

During the following week the rash did not extend, but at points of decubitus pressure a deepening necrosis threatened in some of the haemorrhagic areas, especially on the olecranon and gluteal parts. Anything more than temporary pressure indicated a special susceptibility to subcutaneous tissue damage. The swollen joints gradually subsided in about ten days. No nodular swellings occurred. Fortunately there was no spread of the conjunctival eruption to the ocular structures, and although the facial swelling cleared slowly the clinical course of the illness was markedly abating after fourteen days. A mild, simple albuminuria quickly cleared. This boy had no signs of urethral or genital affection, although it is possible that a transient melaena occurred in the earliest phase. Penicillin, 15,000 units three-hourly, was given over a period of ten days, with the primary object of preventing or combating secondary coccal sepsis. (See figs. 1 and 2.)

**Case 2.** A boy aged seven years entered into an acute illness with high fever, restlessness, and moderate delirium. His eyes and mouth quickly became sore. Dysphagia and cough were troublesome. Difficulty in micturition was associated with acute bullous eruption in the visible urethra and prepuce, with considerable local swelling. Five days from the first symptoms the boy was intensely miserable, the eyes, mouth, and skin being distressful, and in fact all the visible mucous membranes were in acute exudative eruption. The clinical impression was, however, that the boy was not dangerously ill, as he appeared unexpectedly alert on occasions. The skin showed erythematous patches varying in size from $\frac{1}{4}$ in. to $\frac{1}{2}$ in. and of irregular shape with central vesicle, and being principally disposed on the limbs and the face, the scalp and back being significantly free. Both anterior and posterior surfaces of the limbs were affected and a few papules were present on the hands and feet. Most of the skin lesions blanched on pressure. There was bilateral purulent conjunctivitis with the lids encrusted with thick purulent exudate, but the cornea and other ocular structures did not appear to be involved. Some bleeding foci were seen in the nasal mucosa, and the mouth presented membraneous sloughs, especially on the inner cheeks and tongue, which bled easily on local swabbing. There was no visceral abnormality. Blood count was quite normal, and there was no eosinophilia. After six days the exudative reactions showed early resolution, but dysphagia proved troublesome owing to the pain and immobility of the oral structures. Penicillin, 20,000 units at three-hourly intervals, was given as a protective measure, although no pyogenic bacteria were found in the nasal or oral material. (See figs. 3 and 4.)

## Discussion

The varied and somewhat bizarre descriptions surrounding the disease type initially recorded by Hebra are an indication of the many ways in which clinical description may differ when dominant manifestations may be present in distinctive tissues. The ' scattering ' in medical literature is no doubt due to the variety in leading signs, which is probably in reference to the factors of primary virus infection, special tissue reaction (especially ectodermal), anaphylactic-like phenomena, and secondary sepsis. In the form of erythema under review some importance is attached to clinical accuracy, especially in regard to possible ocular, oral, or cutaneous resemblance to other conditions. Special difficulty may arise when, as is sometimes the case, the skin effects are minimal and the clinical state is essentially that of acute involvement of the mucous membranes of the mouth and of the conjunctiva. Panophthalmitis with perforation of the eye must be regarded in nearly all cases as the worst possible danger, and especially so in young children. The absence of vesicular or bullous changes and the quick variations in distribution should distinguish E. marginatum. Polymorphous rashes, usually about joints, but sometimes with a more generalized tendency and a secondary haemorrhagic appearance with minute vesicles, are observed in the Henoch-Schönlein syndrome. It is of considerable interest that, in one case, joint swellings were recognized during the acute phase of the illness. There was, however, complete absence of any abdominal symptoms.

The condition of the membranes of the mouth may cast a possible suspicion of diphtheria, although the bullous changes in the mucous membranes and lips clearly dispose of the possibility.

Perhaps some resemblance may exist in regard to variola, and in fact confusion has occurred occasionally. Certain atypical forms of smallpox may have to be considered when papular lesions, however few, quickly acquire vesicular, pustular, or haemorrhagic changes, and especially when such lesions are disposed more particularly about the face, forehead, backs of the hands and feet, and the wrists. Increasing familiarity with the syndrome of E. multiforme of the type discussed in this paper should, however, soon dispose of essential difficulty. Although many of the patients pass through their illness without significant danger, careful watch must be kept on certain possibilities, and probably in the order of importance as (1) conjunctival disease spreading to the ocular structures, (2) progressive ulceration in the mouth favouring descending respiratory sepsis, (3) pressure effects on the skin leading to a deepening necrosis.

**Treatment.** It is in relation to these more severe possibilities that treatment is particularly directed to the affected mucous membranes and the eyes.

Whilst penicillin probably has beneficial action against secondary staphylococcal infection, sulphonamides are better avoided in view of the aggravating effects which have been strongly suspected in some of the cases reported. Neller noted that sulphamezathine was without favourable effect in the severe phase, but general improvement followed penicillin intramuscularly. In a boy bearing the clinical features of E. multiforme bullosa, with marked oral and ocular signs, the disease was apparently aggravated by sulphathiazole, and, in fact, this was considered to be the determining factor in the fatal termination. Nicotinic acid therapy is considered favourably by Weisberg and Rosen (1946).

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# CASE REPORTS

## CONGENITAL SKIN DEFECT OF THE NEWBORN

BY

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William Campbell (1826) published the first account of congenital skin defect of the newborn. The two patients he described were infants of the same family, the lesions affecting the scalp in each case; both infants died, one from haemorrhage on the eighteenth day, and the other from hydrocephalus at nine months; in the latter healing had begun before birth.

Jones (1849) described a patient with a defect extending from the third dorsal vertebra across the scapula and along the dorsal surface of the arm to within an inch of the elbow. Near the commencement was a nipple-like process of skin, and immediately beyond this healing had begun.

Since that time a number of cases have been reported in the literature, and Terruhn (1930) was able to collect seventy-nine in which the scalp was involved and twenty-nine involving other sites. Cases occurring subsequently have been reviewed by Freud et al. (1945).

The following three examples of this unusual skin defect have been seen in the past year, and it is considered that they are worth recording.

### Case Histories

**Case 1.** R.C.M. was a full-term child born of healthy parents on March 7, 1947. Labour was normal, and there was no history of injury during pregnancy. There had been seven previous pregnancies: all of these children are now alive and well, and have no congenital malformations. The third child had been born two months prematurely and weighed only two and a half pounds at birth.

The midwife noticed an abnormality of the scalp and showed it to the mother a few minutes after birth: the child was not seen by us until three weeks later, and the mother stated there had been no material change during this time. There was a large skin defect on the vertex of the scalp behind the anterior fontanelle, extending more to the left than the right of the mid line, and roughly oval in outline, measuring seven by five cm., the larger measurement being antero-posterior; the edges of the lesion showed evidence of healing, and the remainder was covered by a scar. There appeared to be a defect in the skull under this region, and radiologically this was shown to involve the left parietal bone and to a lesser extent the right. Anterior to the large lesion there were two smaller ones a few millimetres in diameter.

To the left of the skin defects a large dilated vein was visible below the normal skin and extending the whole length of the skull.

The blood Wassermann reactions of the mother and child were negative.

Subsequently healing progressed steadily. Portions of the scab fell off from time to time with consequent healing. By four months healing was complete with hair growing over much of the area.

**Case 2.** Baby S. was born six weeks prematurely on April 4, 1947. Labour was normal, and there was no history of injury during the pregnancy. There had been one pregnancy two years previously, and this child is alive and healthy with no congenital malformations. During pregnancy the mother had been healthy, and physical examination revealed no abnormality. Four years previously partial thyroidectomy had been performed because a large thyroid had caused respiratory embarrassment. The father also was healthy but he too had a partial thyroidectomy four years previously on account of thyrotoxicosis. An exhaustive family history failed to reveal any evidence of congenital malformations.

The appearance of the infant was striking. The skin was absent over the tip of the nose, the tips of both ears, and the adjacent area of the right occipital region. It was also absent over the dorsal surfaces of the hands and both surfaces of the wrists, and over the dorsum of the feet and anterior surface of the legs, knees, and lower thighs. The calves were covered with skin but the ankle regions were bare; skin was present over the palms of the hands and soles of the feet.

In the areas where the skin was lacking there was a membrane which was quite transparent at birth so that vessels, nerves, tendons, and muscles could be viewed clearly through it. During the course of the next few days this membrane was converted into a scab. No other congenital abnormalities were discovered, but the child's general condition was poor and it died on the fifth day in spite of

receiving all the care given to a premature infant. The blood Wassermann reactions of father, mother, and infant were negative. The specimen was preserved intact (figs. 1 and 2) and necropsy was not performed.

The infant measured, from crown to rump, 29 cm. The lesions measured:

| | |
|---|---|
| Left arm and hand (dorsum) .. | 6·3 cm. |
| Right arm and hand (dorsum) .. | 6·3 cm. |
| Left thigh (anterior) to patella .. | 5·7 cm. |
| Left patella to left external malleolus .. .. .. | 8·2 cm. |
| Left external malleolus to extremity .. .. .. .. | 5·0 cm. |
| (The right leg was similar) | |
| Right occipital region .. | 2 by 1·5 cm. |
| Tip of nose .. .. | 1·2 by 1·2 cm. |
| Lateral surface right elbow | 0·6 by 0·6 cm. |

HISTOLOGICAL EXAMINATION. A portion of skin was removed from the right forearm which included the transition from normal to bare area. Microscopically it showed complete absence of epidermis and epidermal structures over the affected area, the change from the normal being clearly marked; subcutaneous fat disappeared at the same point as the epidermis. The dermis remained intact, and as the subcutaneous fat was missing the dermis rested directly on the underlying muscle; blood vessels in the dermis were slightly dilated, and there was a mild infiltration with inflammatory cells, lymphocytes, and neutrophile polymorphonuclears (figs. 4 and 5).

Case 3. G.C. was not seen by us until he was two years old. He had an area of cicatricial alopecia on the vertex of the scalp slightly to the left of the mid line in the region of the lambda and measuring 5 by 2·5 cm.; there was no telangiectasia in connexion with it (fig. 3). The child also presented a much larger area of partial alopecia resulting from trichotillomania; mentally he was backward, but physically he appeared normal except for the skin lesion.

The mother said that at birth there had been a scabbed area on the scalp, much larger than the present scar, which had healed quite rapidly and much of it was soon covered with hairs. Birth had occurred at full term but it was a difficult breech delivery. The child weighed 7 lb. at birth, and throughout pregnancy the mother had been healthy and had not had any injury. There had been no other pregnancies and as far as could be ascertained there was no family history of other congenital malformations.

Blood Wassermann reactions of mother and child were negative.

## Discussion

Congenital skin defect of the newborn is a rare abnormality affecting the scalp in the majority of cases; the lesions appear early in intra-uterine life and have been noted in a four-month foetus (von Hoffmann, 1885). Ingalls (1933) described lesions seen in embryos as early as the second month and which he believed would have developed into the typical defect.

It is unusual for the abnormality to extend deeper than the epidermis, but on the scalp all structures down to the dura may be involved (Kehrer, 1910). The child may be stillborn or it may have other congenital malformations.

Clinically the condition at birth may show a raw granulating surface or it may be covered with a crust. Occasionally there may be a bulla or there may be a thin transparent membrane; healing may have started before birth. Later in life the condition shows as a scar.

Histologically there is a complete arrest of development of all layers of the epidermis and its associated glands and hair follicles (Emanuel, 1906). At the edges of the lesion the defect may be less severe, so that the final patch of alopecia is smaller than the raw area at birth.

The etiology of the condition is uncertain; an hereditary factor is present in a few cases (Campbell, 1826; Freud et al., 1945), but in the majority no such history can be obtained. There are two main views as to causation. The older maintains that it is due to amniotic adhesions; as a result of plastic inflammation of the amnion and epidermis, these grow together and cause arrest of growth of the epidermis. Later as the amniotic fluid increases, the two are forced apart and bands are formed; foetal movements assist in the separation, and the bands may separate entirely before birth. This theory is upheld by Kehrer (1910) and Terruhn (1930); the latter author describes one case in which such adhesions were present at birth, and shows with diagrams how the skin defect could be produced.

The second theory was advanced by Greig (1931) and amplified by Ingalls (1933). These writers believe the condition is due to an arrest of development; in favour of this is the usual mid-line position on the scalp, the striking symmetry in other areas, and the association with other congenital defects. Ingalls pointed out that the dorsal mid line, especially of the scalp, is subjected to important rearrangements during development so that abnormalities are most likely to be found here. He also points out that whilst the foetus is surrounded by fluid there is little tendency for the lesions to heal but that healing occurs rapidly after birth. A few cases may be the result of injury in utero (Kehrer, 1910) but many are not so caused, for mechanical injury would not be limited to the epidermis.

In reviewing the literature one is informed of the great similarity of cases. On the scalp they are

usually small and situated in the mid line of the vertex. On the trunk, lesions described by Hochstetter (1894) and Sutton (1935) are almost identical; whilst on the limbs the defects of the skin of the knees in the cases of Braun (1894) and Abt (1917) are similar. Our second case was similar to the one described by Rogatz and Davidson (1943).

No history of rubella or other infection was obtained in any of our cases, and it is our opinion that the condition is a congenital malformation possibly due to a failure of development of the superficial blood vessels over the affected area.

## Summary

1. Three cases of a congenital ectodermal defect of the newborn are described.

2. The literature is reviewed, and theories of causation are outlined.

Our thanks are due to Dr. C. D. Evans for permission to publish Cases 1 and 3, to Dr. P. Phillips, Medical Superintendent, Southmead Hospital (Case 2), and to Professor Yoffey for encouragement and advice.

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FIG. 1.—Case 2.

FIG. 2.—Case 2.

FIG. 3.—Case 3.

FIG. 4 (below.)—Case 2. Low power, showing loss of epidermal structure and subcutaneous fat.

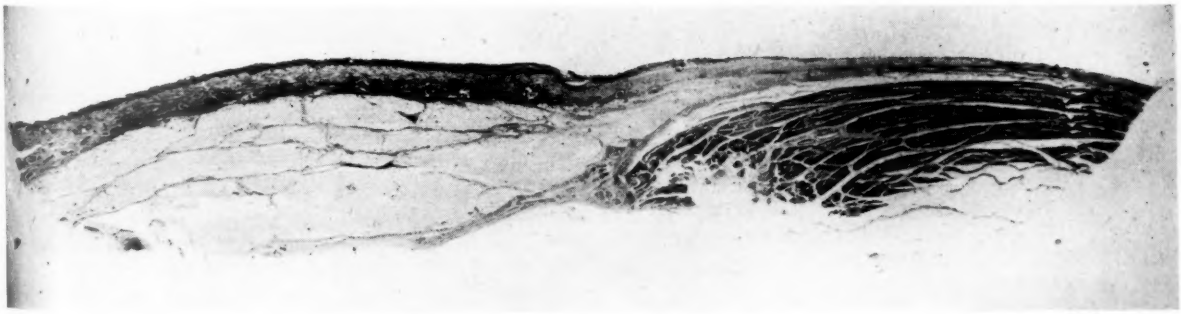

PLATE VI

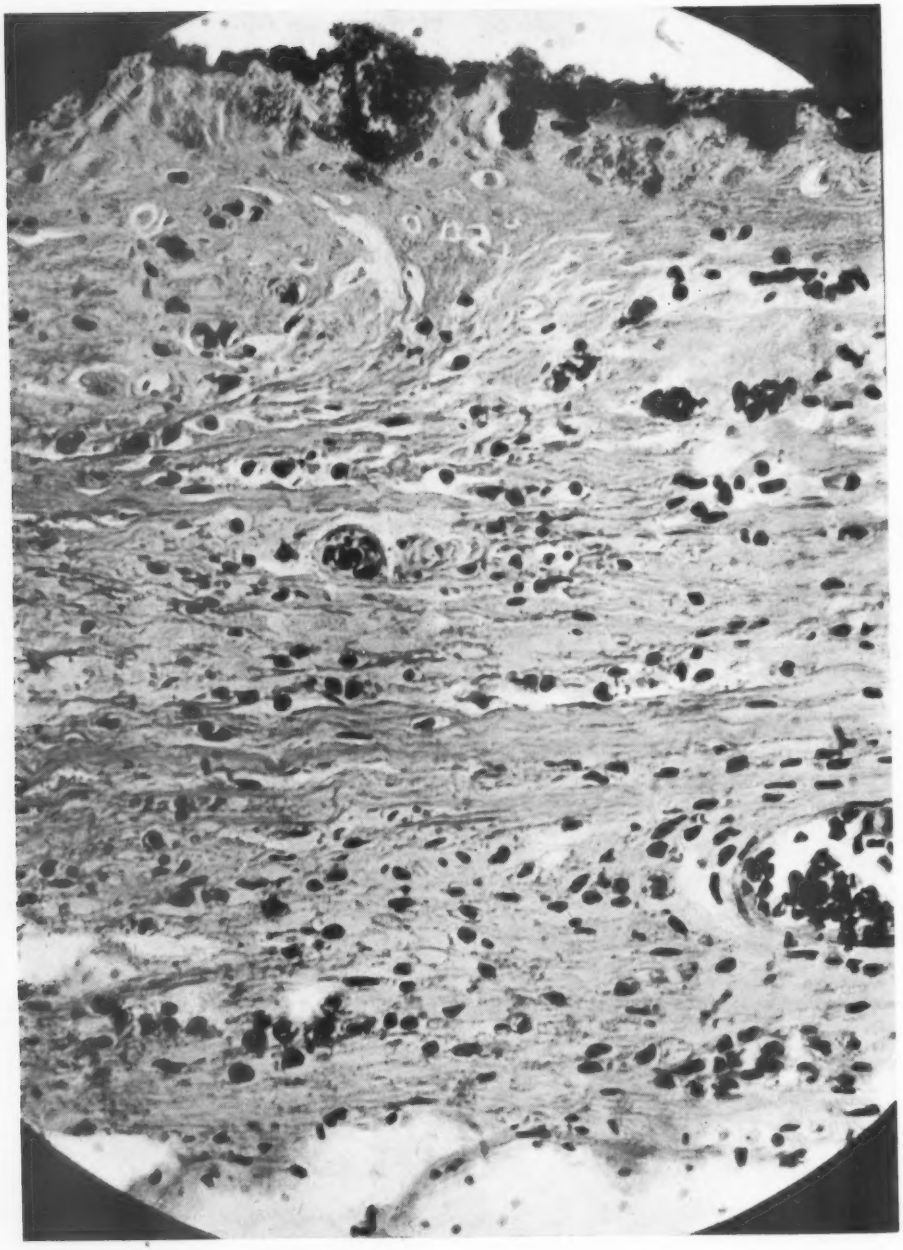

FIG. 5—Case 2. High power at point of transition showing last vestige of epidermis and infiltration of corium with leucocytes and lymphocytes.

PLATE VII

# A CASE OF LYMPHOSARCOMA OF THE INTESTINE IN A CHILD

BY

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Lymphosarcoma of the intestine is a rare disease in children and especially in those of British race, to judge from the dearth of case reports in this country, but the incidence appears to be higher in America since it is the American literature that furnishes most of the examples published in the past fifty years.

The present case is reported since it combines unusual intestinal and renal lesions.

## Case Report

The patient was a boy aged 10¾ years admitted to the Royal Hospital for Sick Children, Glasgow, on Sept. 29, 1944. Tonsillectomy at the age of five years and measles and chickenpox in early childhood were the only items of note in the history, and he was an active, intelligent boy before the present illness which began some six weeks before death with pallor and listlessness, accompanied by pain in the knees and face. A fortnight later he had a single transient attack of abdominal pain without vomiting, of which there are no available particulars. His face shortly afterwards began to swell, and x-ray examination revealed tumour-like nodules in the skull. From about mid-September onwards he was confined to bed suffering from headache, sleeplessness, anorexia, and weakness. The bowels were regular throughout, and there was no dysuria.

On admission to hospital he was a pale, emaciated, acutely ill child with marked muscle wasting, loss of tendon jerks, and pitting oedema of the ankles. The abdomen was swollen and tense, the superficial veins were dilated, and a large, firm, nodular mass, tender to palpation, was present in the hypogastrium and right iliac fossa. The kidneys and spleen could not be defined but the smooth edge of the slightly enlarged liver was palpable below the costal margin. No shifting dullness was elicited, and there was no visible peristalsis. The lungs and heart were normal. Soft swellings were found over the vertex of the skull and in the lower jaw. There was a right-sided facial paralysis and the left eye was slightly proptosed. Both pupils reacted to light and on accommodation, and the fundi were normal. His blood on the day after admission had 58 per cent. haemoglobin, a red cell count of approximately 5,000,000 per c.mm. of blood, and a leucocytosis of some 16,000 per c.mm. Ring staining was the only abnormality in the red cells. On differential count neutrophile polymorphs numbered 57·5 per cent., lymphocytes 33 per cent., monocytes 6 per cent., and immature cells of myeloblastic type 3·5 per cent. The urine was examined several times and showed merely a trace of albumin, with a few granular casts and leucocytes. The bowels were regular. There was rapid deterioration in the child's condition with increasing asthenia, and death occurred five days after admission.

**Autopsy.** An autopsy was performed next day. The subject was well grown for his age but pale and extremely emaciated. There was no noteworthy enlargement of the glands in the neck, axillae, and groins. The long bones were all normal in contour, but swellings were palpable in the vault of the skull, and a nodule composed of pale, soft, tumour tissue was present in the left lower jaw in the gap left by two missing premolar teeth. The soft tissues but not the bone were invaded. No appreciable proptosis of the left eye was observed, and periorbital haemorrhage was absent. No tumour deposits were seen in the atrophic thymus, in the mediastinal lymph glands, or in the lungs. Both pleural sacs were normal. Many small, pale, sub-epicardial tumour nodules were present anteriorly in the normal-sized heart, projecting slightly above the surface. The scanty pericardial fluid was pale yellow and clear.

Below the diaphragm the picture was striking owing to the presence of large tumours which involved the abdominal glands, the mesentery, omentum, kidneys, and intestines. The root of the mesentery was occupied by a bulky, nodular neoplasm composed of fused mesenteric glands; a few nodes at the periphery remained discrete and these were greatly enlarged. On section of this tumour the cut surface was pale and homogeneous and the texture soft and brain-like. A smaller glandular mass of similar type and showing central haemorrhage was present in the ileo-caecal angle. In addition, the entire mesentery was loaded along the course of the lymphatics with innumerable small, discrete tumour-bearing glands. There was widespread infiltration of the omentum with great increase in bulk. The stomach itself was of normal size and contained only three small, flat, sessile

tumour nodules on the mucosa, two near the cardia and one on the lesser curvature close to the pylorus. It was, however, in the lower gastro-intestinal tract that tumour growth was most exuberant. The duodenum was tumour-free, but from the duodeno-jejunal junction to within a few feet of the terminal ileum the wall of the small bowel was heavily loaded with tumour tissue which had infiltrated especially the circular folds of the mucosa and had expanded them into thick, prominent ridges. The Peyer's patches were converted into large flat plaques, some showing superficial ulceration. All the tumour nodules were sessile and by their annular mode of spread had stretched the bowel so that the lumen was widely patent and was not obstructed (fig. 1). Some six feet above the ileo-caecal valve, tumour growth ceased rather abruptly, and the terminal ileum was normal in appearance and calibre.

A massive tumour, which was regarded as the primary growth, occupied the caecum with great thickening of the wall, but central ulceration had taken place and here again there was no obstruction. Intramural haemorrhage with necrosis had occurred, and rupture was imminent, but there was no trace of peritonitis to indicate antemortem leakage of intestinal contents. The rest of the large bowel was normal in all respects.

The kidneys (fig. 2) presented a remarkable appearance from their resemblance to large bilateral renal tumours, though retaining their reniform shape and smooth surface. In fact, they consisted chiefly of neoplastic tissue which permeated the organs in all parts and replaced their normal structure by pale, homogeneous tissue flecked by small haemorrhages. The cortex on each side was greatly widened, and overgrowth of the inter-pyramidal zone had forced apart the small, pale-red calyces. The capsule on each side was infiltrated and thickened by tumour growth. Both renal pelves and ureters were normal. The spleen, liver, adrenal glands, pancreas, and gallbladder were all free from metastases.

Widespread skeletal deposits were present, notably in the bones forming the vault of the skull, where nodules of varying size arose both in the inner and outer tables. A mass growing from the left parietal bone projected inwards and indented the underlying cerebral cortex in the motor area, thus accounting for the right-sided facial paralysis observed during life, but there was no invasion of the brain or meninges. No tumour nodules were found in the base of the skull or in the orbital cavities. Metastases were present in several of the lower dorsal vertebrae, and one or two ribs had minute, flat, button-like nodules on the periosteum, but the pelvic bones were tumour-free. The marrow cavity of the right femur was filled by pale, tumour-like tissue, but there was no sub-periosteal infiltration.

**Histology.** Paraffin sections were prepared and stained by a variety of methods, including haematoxylin and eosin, iron haematoxylin and van Gieson, the Romanowsky method published by Barrett (1944) and the reticulin stain described by Lendrum (1947).

The primary growth and the secondary deposits in various tissues showed an identical homogeneous structure consisting almost entirely of lymphoblastic cells. The individual tumour cells were round or oval with a relatively large, pale, vesicular nucleus surrounded by a narrow basophile-staining protoplasmic rim. The nuclear chromatin formed a delicate lightly-stippled network which stained much less densely than in the mature lymphocyte. A single nucleolus was frequently present but in many cells none could be demonstrated by any staining method. Mitoses were fairly numerous but multinucleated giant cells were scanty and there was no noteworthy inflammatory cell component. There was no attempt at follicle formation and the cells were arranged in the form of a loose mosaic. Collagenous stroma was scanty and there was little attempt at reticulin formation on the part of the tumour cells which appeared rather to have invaded and destroyed the normal pre-formed reticulin than to be laying down new fibrils. This marked capacity to invade and destroy all normal tissues in its advancing path was a feature of the growth. It was well supplied with thin-walled blood vessels and there were few areas of necrosis.

Sections of the caecal tumour (fig. 3) showed massive invasion of the mucosa and submucosa. These coats were densely packed with lymphoblasts and greatly thickened, but it was still possible to distinguish the muscularis mucosae. The delicate processes of the mucous membrane were converted into massive, club-like structures, many necrotic at the tip, and the glands of Lieberkühn were widely separated, small, and atrophic, while some had undergone cystic degeneration. Both the circular and the longitudinal muscle coats, which were of about the normal width, were extensively infiltrated and fragmented by the invading tumour cells, and these had reached the serous surface. In some of the smaller lymphoid nodules in the small intestine, tumour infiltration was confined to the mucous and submucous coats. In the kidneys the capsule was thickened by tumour growth and the degree of interstitial invasion was extreme with almost complete destruction of the glomeruli and tubules in some areas. Surviving renal structures were small, atrophic, and isolated in a mass of lymphoblasts (fig. 4). Other portions of the cortex were fairly well preserved, but even in such relatively intact areas tumour cells were present in smaller numbers and had penetrated between the tubules. By contrast, the medullary zone was relatively tumour-free. In the lymph glands the normal structure was replaced by diffuse cellular infiltration without follicular arrangement. Skeletal metastases were of similar uniform type, with replacement of the heterogeneous components of the normal marrow by the homogeneous tumour cells. Nodules in the heart wall were composed of dense, lympho-

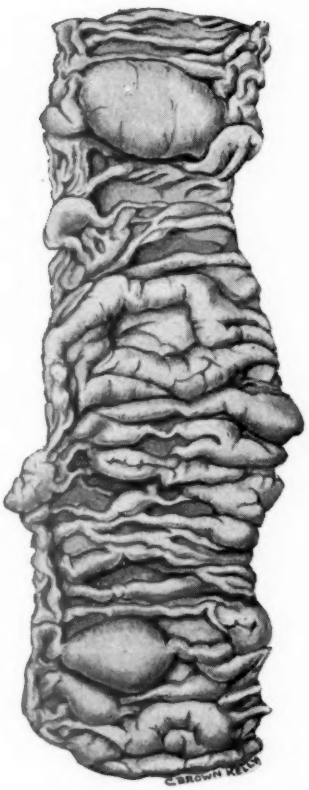

FIG. 1.—Dilated small bowel loaded with nodules of lymphosarcoma. (Half natural size.)

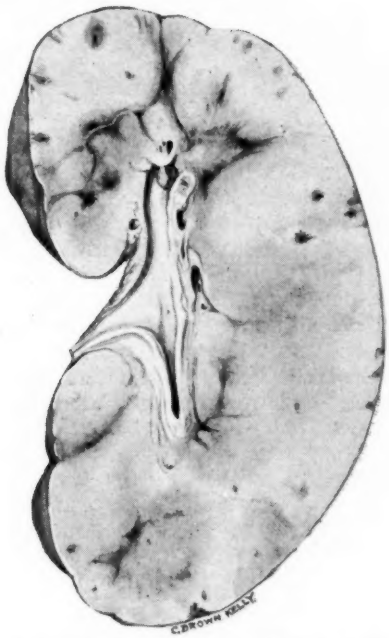

FIG. 2.—Enlarged kidney showing diffuse lymphosarcomatous infiltration. (Half natural size.)

FIG. 3.—Caecum permeated by lymphoblastic cells with great thickening of mucous and submucous coats. (×15.)

FIG. 4.—Kidney showing diffuse interstitial infiltration by tumour cells with few surviving glomeruli and tubules. (×180.)

PLATE VIII

blastic collections which had invaded the epicardium and spread along the interstitial planes of the myocardium with loss of the muscle fibres.

## Discussion

Since Ewing (1913) first suggested the derivation of certain lymphoid tumours from reticulum cells, the term reticulosarcoma has been employed with increasing frequency in the literature. A detailed classification is given by Robb-Smith (1938) of the various types of tumour arising in reticulum cells at all transitional stages from the primitive syncytial reticulum to the mature lymphocyte. Willis (1948), however, regards these several types of tumour not as rigidly distinct species, but as related variants of a single species, and would restrict the term reticulosarcoma to tumours where differentiation of reticular tissue is distinct and predominant. In the present case the lymphoblastic cells composing the tumour were deficient in reticulin formation, and it has been classified accordingly as a lymphosarcoma of lymphoblastic type rather than as a reticulosarcoma. Uniformity of cytological structure is characteristic of lymphosarcoma. Boyd (1947) regards this feature as outstanding, and Willis describes the structure as composed of ' diffuse masses of rounded cells of uniform size. . . . The cells penetrate into all the available interstices of the invaded tissue, whether kidney, liver, intestine, heart wall, lung or lymphoid tissue itself, mingling inextricably with the surviving components of these.'

Intestinal lymphosarcoma is rare at all ages. Warthin (1915) found only two examples in an analysis of 2,000 malignant neoplasms, and it is even more uncommon in early than in later life, although youth and even infancy are not entirely exempt. A congenital case is recorded by Stern (1901), and Ewing (1922) states, ' Not a few lymphosarcomas arise in infants and appear to have a congenital basis.'

The disease is twice or thrice as common in males as in females. Much of the literature on intestinal sarcoma, both old and recent, is of American origin. Thus, Libman (1900) reports five cases of his own, two in children, aged respectively 3½ and 12 years. This author also collected from the literature fifty-one cases, of which six occurred in the first and nine in the second decade. Jopson and White (1901), also in America, describe a case in a child aged 4 years. Cutler et al. (1945) of the Harvard Medical School, record five cases arising primarily in the bowel in children aged respectively 4, 21, 64 and 66 months, and 7 years. They state that neoplasms of the small and large intestine are extremely rare in children as compared with adults. Simpson-Smith (1938), who publishes one of the few British series, found only six examples of abdominal sarcomata in the records of the London Hospital for Sick Children dating back to 1900, and on making an exhaustive search of the world literature as far back as 1852 he discovered only a hundred similar cases in children, the maximum incidence falling between the ages of 1 and 5 years, with five cases in infancy and two of these in the neonatal period. Of these 106 tumours, seventy involved the small intestine and most commonly the ileum; thirteen arose in the caecum, six in the appendix, and the rest in various parts of the colon. Ewing (1922) and Ullman and Abeshouse (1932) also found the ileum the site of predilection. Willis remarks that in cases presenting as generalized lymphosarcomatosis the site of origin is not always clear, but where a large tumour of a particular region is present this suggests, but does not always prove, that the tumour began in this region. In our case the large, nodular mass in the caecum, palpable during life, is believed to represent the primary growth, since by analogy with the sequence in abdominal tuberculosis, where infection spreads from the bowel along the mesenteric lymphatics, it appears more likely that the tumour had originated in the intestine and extended along the lymph paths draining into the root glands, than that it was primarily glandular with retrograde spread to the bowel.

Rapid and extensive metastasis is the rule in lymphosarcoma since this type of tumour is characteristically of multicentric origin, arising not in a single lymph node, but simultaneously in groups of nodes or in multiple lymphoid foci in a mucous membrane like that of the small bowel, and is capable of spreading with great rapidity along submucous surfaces. In the later stages dissemination occurs also by way of the lymphatics and the blood stream. In the case under discussion lymphatic spread in the mesentery was clearly demonstrated, while skeletal metastases were undoubtedly blood-borne.

The disease is seldom arrested, and death generally occurs within a few months of onset. Occasionally its clinical course is hyper-acute, not exceeding twenty-four hours. Thus in three of Libman's five cases the clinical picture suggested appendicitis. In one of these there was only a single day's history of right-sided abdominal pain, and laparotomy revealed a perforated jejunal sarcoma with escape of intestinal contents. Ewing (1922) quotes Birch-Hirschfeld's case, rapidly fatal, which followed typhoid fever and was practically a continuation of typhoid hyperplasia. In Simpson-Smith's series of 106 juvenile cases, over 60 per cent. died within six months, and 92 per cent. within one year of diagnosis. Munson and Marx (1946), however, believe that the outlook is apparently good after surgical removal of a solitary tumour. They record such a case in a boy aged 10 years who remained well after operation, but the period of observation was only two months. In the present case the total duration of illness was six weeks.

Apart from the presence of a tumour there is generally little in the clinical picture to suggest an intestinal lesion, since lymphosarcoma, in marked contrast to carcinoma, rarely obstructs the bowel but, as in the present case, generally expands it.

Ullman and Abeshouse attribute dilatation to destruction of muscle fibres combined with early loss of the nerve plexus in the submucosa. In our case it is remarkable, in view of the extensive intestinal tumour growth, that there were no clinical symptoms of alimentary disease apart from the single, brief attack of abdominal pain soon after the onset of illness. It is known, however, that in adults with excessive lymphoid hyperplasia of the intestinal tract, clinical symptoms may be very meagre, provided there is no intestinal obstruction or ulceration (Wells and Maver, 1904). Simpson-Smith, on clinical analysis of his material, found two facts of diagnostic importance: the high incidence of palpable abdominal tumour, and general deterioration with loss of weight, pallor, and exhaustion, all features of the case under discussion.

In view of the indefinite history and the rarity of intestinal neoplasms in childhood, it is not surprising that few diagnoses are made on clinical findings alone. Only two of ninety-one cases collected by Ullman and Abeshouse were correctly diagnosed without x-ray examination or biopsy. Occasionally lymphosarcoma of the bowel, especially the polypoid variety, presents as an intussusception. Thus in the series reported by Cutler et al., lymphosarcoma had induced intussusception in three cases, including the youngest, an infant aged 4 months. In Kasemeyer's (1912) series of 284 intussusceptions due to tumour, twenty-six had lymphosarcoma as the starting point. It is extremely rare to find multiple lymphoid tumours of the small bowel in childhood, though a somewhat similar condition with multiple foci of lymphoid hyperplasia is described in adults under the name of pseudo-leukaemia gastro-intestinalis. Here the mucosa of stomach and bowel is greatly thickened and thrown into large folds resembling cerebral convolutions. Such cases are recorded by Wells and Maver, and Biggs and Elliott (1924). In true lymphatic leukaemia, also, widespread infiltration of the gastro-intestinal tract may occur, as described by Boikan (1931) and Pearson et al. (1943). These cases generally show an associated lymphoid infiltration of lymph glands and viscera.

The kidneys in the present case presented a remarkable appearance and resembled symmetrical bilateral renal tumours. Ewing (1922) states that the kidney is a favourite seat of metastasis in lymphosarcoma, which may take the form of minute foci, diffuse infiltrations, or bulky masses. Most of the scanty recorded cases of massive renal involvement are in men or youths. Thus, Symmers (1918) saw examples of massive symmetrical enlargement of the kidneys in three cases of lymphosarcoma, all in men, in two of whom the thymus appeared to be the site of origin, while in the third the small bowel had multiple annular tumours. Cohnheim (1865) describes a similar renal lesion in his original adult case of pseudo-leukaemia. Bilateral renal enlargement closely similar to that under discussion is recorded by Turner (1878) in a boy of 15 with a lymphosarcoma of the thymus and general glandular and splenic enlargement. He aptly compares the creamy-white colour of the tumour growth to that of a parsnip. Gouget and Thibaut (1911) saw massive renal infiltration in lymphatic leukaemia in a boy aged 16 with enlarged cervical glands and a growth in the mediastinum. Both organs were of uniform whitish colour with petechial haemorrhages and resembled bilateral tumours as in the present case. All these authors remark on the fact that the urine was normal, except for a trace of albumin and sometimes the presence of a few granular or hyaline casts and epithelial cells.

The blood picture in our case showed no evidence of lymphatic leukaemia, even in the terminal stage, but the close relation between lymphosarcoma and lymphatic leukaemia is well recognized. Gall and Mallory (1942), in a large series of cases, frequently saw the development of lymphatic leukaemia in patients with lymphosarcoma, and this was found by Cutler et al. in two of their five juvenile cases with intestinal tumours. The similarity of the cellular infiltration in the bowel, glands, and various organs in lymphosarcoma and lymphatic leukaemia, and the close resemblance of the lymphosarcoma cells in the tissues to the lymphocytes in the blood, serve to confirm the near relationship of the two diseases. Willis sums up the position in the dictum, ' Except for the demonstrable presence or absence of malignant cells in the circulating blood, there is no difference between lymphosarcoma and lymphatic leukaemia in either gross or microscopic pathology.'

**Summary**

A case of intestinal lymphosarcoma in a boy is described which proved fatal in six weeks from the clinical onset. At autopsy, widespread tumour growth was found in the intestines, kidneys, mesenteric glands, and bones. Clinical symptoms of gastro-intestinal or renal disease had been negligible.

The diagnosis of intestinal lymphosarcoma should be considered in a child with an abdominal tumour accompanied by rapidly progressive loss of weight, pallor, and lassitude.

Thanks are due to Professor G. B. Fleming for permission to consult the case record, to Mrs. Hamilton (C. Brown Kelly) for the drawings, and to Dr. A. H. T. Robb-Smith to whom sections were referred.

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# ISOLATED (FIEDLER'S) MYOCARDITIS

BY

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Isolated myocarditis, since its description by Fiedler in 1899, has received attention abroad, particularly in America and Germany, but no cases seem to have been recorded in this country. It is hoped that this report may stimulate interest in the disease, which may well be less uncommon than hitherto thought.

## Case History

A boy, aged eleven months, was the second child of healthy parents. The mother had been in excellent health throughout her pregnancy, and the patient was a normal baby born naturally at term, weighing 9¾ lb. He was breast-fed for two months and then given a dried milk mixture. Solids were started at three months, and he sat up alone before six months of age. He experienced no illness until July 27, at the age of nine months, when he refused food and was fretful all night. Next day he was pale and listless and vomited twice. He improved the following day but relapsed the day after, when his doctor could find no definite signs, but put him on sulphonamide (amount unknown, but continued for five days). He remained about the same for several weeks, vomiting most days. During this period he was pale and lifeless but took food fairly well. No dyspnoea was noted, and he was stated never to have been febrile. At no time had he had a cold, and there was no illness in the house at the time.

At the beginning of September he was admitted to hospital. On admission his temperature was 99° F., pulse 130, and respirations 50 a minute. He weighed 19 lb. He was fretful and faintly cyanosed. The throat and ears were normal. There was no distension of the neck veins. The heart was enlarged, the apex beat being half an inch external to the nipple. Triple rhythm was audible over the whole praecordium, and the sounds were of fair quality. No murmurs were heard. The blood pressure was 110/65 mm. Hg. The lungs were resonant throughout, and rhonchi were heard at both bases. The liver was enlarged; the edge, about two inches below the costal margin, was sharp and the surface smooth: it did not appear tender. The spleen was not felt and there was no oedema.

After admission he had periodic attacks of dyspnoea in which he became more cyanosed and suffered from cough. To begin with these attacks lasted about fifteen minutes, but towards the end they became more prolonged and severe. Oxygen administration gave relief. Vomiting occurred at irregular intervals without relation to food, which he took fairly well. The vomiting was never marked until the last twenty-four hours, when dark brown fluid was produced. Throughout his stay in hospital his pulse varied from 116 to 160 per minute and was always regular. The triple rhythm persisted throughout, and the temperature never rose above 99·8° F. He died in a severe dyspnoeic attack on Sept. 14.

**Investigations.** A radiograph of the chest (fig. 1) showed a globular enlargement of the heart. Pericardial paracentesis produced no fluid.

There were 3,810,000 red cells per c.mm.; the haemoglobin was 8·6 g. per cent.; and white cells 9,300 per c.mm.

A trace of albumin was present in the urine, but examination of three specimens disclosed no sugar or acetone. There was only an occasional leucocyte in the deposit.

The large heart and apparently painless enlargement of the liver suggested a diagnosis of glycogen disease; a blood-sugar curve following the injection of adrenaline showed a small rise, as follows:

fasting level 103 mg. glucose per 100 ml.

½ hour after adrenaline, 111 mg. glucose per 100 ml.

1 hour after adrenaline, 108 mg. glucose per 100 ml.

1½ hours after adrenaline, 70 mg. glucose per 100 ml.

With the repeated absence of acetone from the urine, these findings were considered incompatible with such a diagnosis. Blood cholesterol was 228 mgm. per 100 ml.

**Autopsy.** An autopsy was performed within twelve hours of death. Apart from a somewhat protuberant abdomen the body appeared normal. There was no oedema, but 10 ml. of clear, dark yellow fluid were present in the peritoneal cavity. There was no pleural nor pericardial effusion.

The heart weighed 110 g. (normal 40 g.). Both ventricles and auricles were somewhat dilated, and their walls thickened. The endocardium of the left auricle was grossly thickened. The myocardium was bright red and was rather hard in consistency. No mural thrombi nor vegetations were present, and the valves were normal, though the chordae

tendineae of the mitral valve appeared unusually short. There were no congenital defects (fig. 2).

The liver (390 g.; normal 277 g.) showed the appearance found in chronic venous congestion. The spleen (30 g.) was firm and engorged. Apart from a small patch of consolidation on the anterior border of the right lower lobe, the lungs showed only engorgement; there was no pulmonary oedema.

The remaining organs were found to be within normal limits.

**Histology.** A complete histological examination was carried out. In view of the suspicion of glycogen disease, portions of liver, kidney, and pancreas were fixed in alcohol and stained specifically for glycogen. None was found.

Sections were cut from all four chambers of the heart, from the mitral valve, and from a papillary muscle of the left ventricle. They all showed the principal histological lesion, a diffuse infiltration of the myocardium by lymphocytes. In places this infiltration was somewhat focal, and in these areas there was some degree of fragmentation of the muscle fibres. The muscle cells were little altered and their nuclei were normal. There was a moderate interstitial oedema. In none of the sections was there any granulomatous tissue, and no polymorphs, plasma cells, or tissue cells took part in the infiltration. No Aschoff nodes were present. The endocardium of the left auricle was grossly thickened but the lymphocytic infiltration did not occur in it. No vegetations were on the mitral valve, and its fine fibrillary pattern was not distorted (figs. 3 and 4).

Sections of the liver confirmed the diagnosis of chronic venous congestion. No evidence of infection was found in the intestine or lungs, and the patch of consolidation appeared to be a small thrombotic infarct.

## Comment

The histology of isolated myocarditis is described, among others, by Saphir (1942), and Saphir, Wile, and Reingold (1944). They recognized two types, the diffuse lymphocytic, and the granulomatous. In only one respect did the present case differ from the classical lymphocytic form, namely in the thickening of the endocardium of the left auricle. In fourteen cases the latter authors gave a full histological description, and in two of these there was endocardial fibrosis associated with a purely lymphocytic infiltration; these were the only cases with this type of infiltration. Thus an endocarditis may be a feature of the condition although it was not included in the classical description.

The histological diagnosis in adults and in the granulomatous types is not so clear. For example Smith and Furth (1943) described three examples but only mentioned the state of coronary vessels in one. Saphir's (1942) description of the granulomatous type included a reference to giant-cell systems, and it is felt that the condition of periarteritis should be excluded in this group.

It is probably safer to reserve the diagnosis of isolated myocarditis for those cases which show the histological lesions of the lymphocytic type.

**Differential diagnosis.** A number of conditions must be considered in the differential diagnosis.

DIPHTHERIA. There seems to be a close similarity in the microscopical changes in diphtheritic myocarditis and Fiedler's disease. In fact Singer (1932) suggested that all these cases were diphtheritic in origin. However, the absence of diffuse hyaline degeneration and any sign of reparative inflammatory process, together with the lack of any suggestive history or clinical finding, make this diagnosis unlikely.

RHEUMATIC FEVER. There was no clinical evidence of this disease, so rare in infancy; and, histologically, there was no endothelial reaction and there was an absence of Aschoff nodes.

An exactly similar myocarditis has been shown to complicate nearly all the common specific fevers. There is no evidence that any of these diseases was present in this case. Poliomyelitis, which has recently been shown (Saphir and others, 1944) to be complicated by similar changes, was excluded by the clinical state and the absence of histological findings in the nervous system.

BERI-BERI. An example of fatal cardiac beri-beri was recorded in England by Allibone and Baar (1946), but the heart in this case showed gross changes in the muscle fibres and no interstitial changes such as were found in our patient.

SULPHONAMIDE MYOCARDITIS. A number of patients treated with a variety of sulphonamide drugs have been found to show myocardial changes (French and Weller, 1942). Although our patient was given sulphathiazole for five days early in his illness the changes are dissimilar to those described in this condition, since neither eosinophils nor large mononuclears took part in the infiltration.

TRICHINIASIS. Interstitial cellular infiltrations similar to those described have been found in patients suffering from this disease. The heart changes are said to occur between the seventh and twenty-sixth days after infestation. No signs of worm infestation were found on examination of the other organs and skeletal muscle, and there was no eosinophilia.

Glycogen disease was eliminated by clinical and biochemical examinations. The poor response to adrenaline may well have been due to the extensive hepatic lesions of chronic venous congestion.

## Classification of Myocarditis

Saphir and others (1944), in their excellent review of the subject, offer the following classification of myocarditis: (1) foetal (of doubtful entity); (2) myocarditis following contagious and infectious

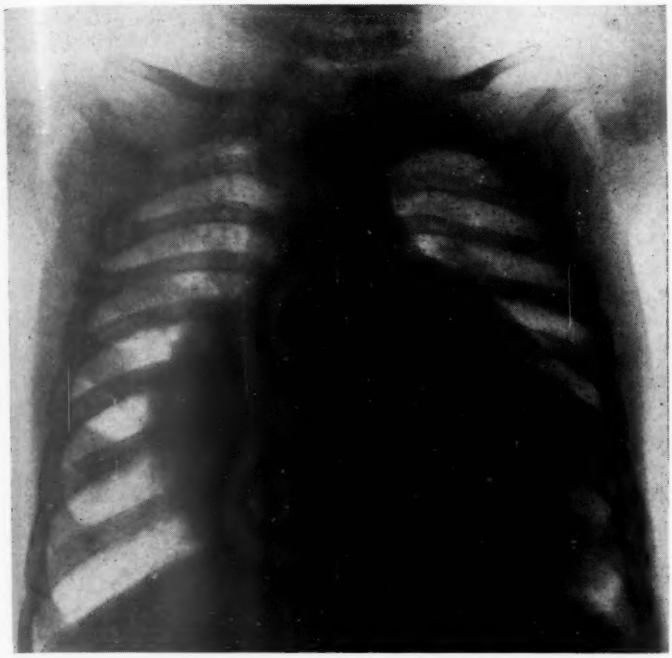

FIG. 1.—Radiograph showing size and shape of the heart.

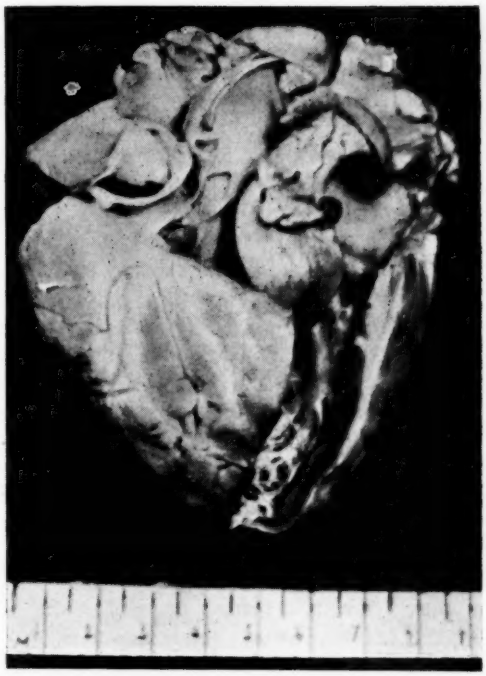

FIG. 2.—The heart, to show size and thickened endocardium of the left auricle.

FIG. 3.—Lymphocytic infiltration without gross degeneration of muscle fibres. × 650.

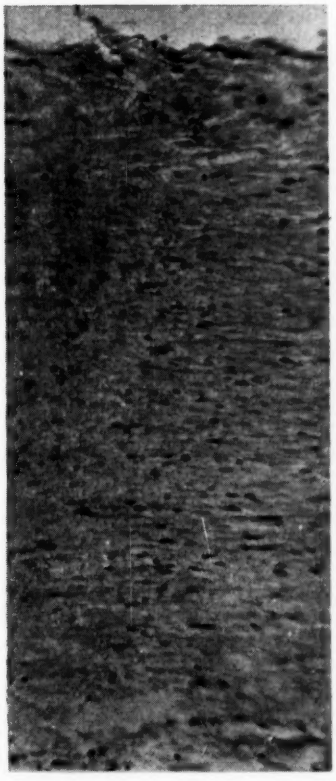

FIG. 4.—Thickened endocardium of left auricle. ×150.

PLATE IX

diseases (a) with endocarditis, and (b) without endocarditis; (3) isolated (Fiedler's) myocarditis; (4) specific myocarditis (rheumatic, tuberculous). They found ninety-seven examples in 1,420 autopsies in a general children's hospital, an incidence of 6·83 per cent. (acute infectious diseases were not admitted to the hospital). Of these ninety-seven, only three were considered to be examples of isolated myocarditis.

The condition may occur in adults and children and most of the recorded cases have occurred in the former.

The diagnosis is difficult, and clinically the cases usually present with increasing myocardial failure for no apparent cause. The temperature is little elevated but tachycardia is constant. Cardiac enlargement and cyanosis are usually seen, and the course is typically rapid with sudden death common, although Baikan (1931) has described acute and chronic types, the latter showing healing and fibrosis. The possibility of resolution of the lesion with a resulting diffuse fibrosis of the myocardium may be considered. Such cases may well include some of the deaths reported in young adults from myocardial fibrosis and regarded as early coronary deficiency.

Conduction changes and alteration of the T waves may be found in cardiograms.

All authorities stress the importance of making careful histological sections of the myocardium, as the changes may be scattered and easily missed if only a few blocks are examined.

The cause of the condition is unknown, though allergy and idiosyncrasy to drugs, arsenic, and (latterly) sulphonamides, have been suggested. Bernheim-Karrer (1923) found the condition associated with infantile eczema and suggested an allergic cause.

Possibly the ill-defined entity congenital idiopathic cardiac hypertrophy may include examples of this disease. No treatment has proved effective; and, indeed, until the cause is found, none of a specific nature can be attempted.

**Summary**

A fatal case of idiopathic (Fiedler's) myocarditis is described. The diagnosis of the condition is discussed and the importance of thorough histological examination of the myocardium in young people who die of unexplained cardiac failure is stressed.

We wish to thank Messrs. D. R. Paton and F. E. R. Byron for help with the photographs, and Miss A. Holding for technical assistance.

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# H. INFLUENZAE MENINGITIS

BY

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The treatment of influenzal meningitis, particularly in a young child, was usually unsuccessful before the introduction of the sulphonamides, serum, and antibiotics. These agents have altered the prognosis, but the choice of one or more of them is not easy, nor is the success attending each invariably predictable. This uncertainty of therapeutic response is much greater in cases which are diagnosed late or have received inadequate treatment. Alexander (1947) says that the sulphonamides, serum, and streptomycin, used singly, are all effective agents in certain circumstances. She concludes, however, that except in special institutions all of them are indicated simultaneously in a severe case, particularly as residual cerebral damage may be less after such combined treatment.

Alexander found that sulphonamide and antiserum were equally effective in protecting mice, but that together they exerted a pronounced synergistic action; she also found sulphadiazine, sulphathiazole, and sulphamerazine of approximately equal efficacy, although she employed mainly the first. Streptomycin was found to be the most potent agent against H. influenzae, though not adequate alone in the most severe infections; its use is limited by its toxicity and by the readiness with which the organism becomes drug-fast (*Lancet*, 1948). She found penicillin relatively ineffective at concentrations usually attained. It is not totally ineffective, however, and the supply of streptomycin and antiserum is so precarious in this country that penicillin is usually employed here. Gordon and Zinnemann (1945) pointed out that many strains of H. influenzae are relatively sensitive to large doses of penicillin. Successful results have been obtained by this means by Forgacs et al. (1945) in one out of two cases, McIntosh and Drysdale (1945), Drysdale et al. (1946), and Gerrard (1947) in single cases, and by Gottlieb and Forsyth (1947) in three out of four cases. Thomson et al. (1947) used sulphonamides with penicillin intramuscularly and intrathecally with three cures out of four. Unlike Alexander, they found no close relationship between the clinical response to a drug and the in vitro sensitivity of the organism to that drug.

The case here reported ran a long course, and was treated with every available drug, with ultimate success. We believe that in this case the administration of anti-influenzal rabbit serum was the deciding factor in bringing about recovery. The findings in the cerebrospinal fluid showed a remarkable difference after the antiserum, which fortifies our belief that recovery thereafter was not coincidental.

### Case Report

M.S., aged sixteen months, had a normal infancy with no illnesses, and was well until Oct. 29, 1947, when he looked cold and vomited his breakfast. He was feverish and refused further food. The following morning he had a temperature of 103° F. and was given 0·5 g. of sulphathiazole, with 0·25 g. four-hourly afterwards. This dosage was maintained for five days and his temperature settled to 100° F. Throughout this period he took fluids well but little food. On Nov. 5 he vomited for the second time, and next day he was admitted to another hospital, where the diagnosis of influenzal meningitis was made and an intrathecal injection of 5,000 units of penicillin was given. This was repeated on Nov. 7 before his transfer to this hospital for streptomycin treatment.

On admission he was a very ill, feverish, flushed child of 21 lb. weight, rather apathetic during examination. No local lesion apart from the nervous system was discovered. The fontanelle was closed, and there was some neck stiffness but no head retraction. Kernig's sign was positive only on the left, there was no photophobia or squint, and the fundi were normal. All reflexes were present, including the abdominals, and the plantars were flexor.

Blood culture gave a growth of H. influenzae, Pittman type B.

Lumbar puncture yielded very turbid fluid, and streptomycin was injected intrathecally. At the same time intramuscular streptomycin was started. The cerebrospinal fluid formed a number of clots on standing, and was xanthochromic after centrifuging. There were 20,560 cells per c.mm., mainly polymorphs, protein was 640 mg. and the chlorides 670 mg., while the sugar was only 8 mg. per 100 ml. Smears showed many pleomorphic Gram-negative bacilli, identified culturally as H. influenzae, type B.

If Alexander's criterion that the cerebrospinal fluid sugar level is the best indication of the severity of a case, then this case was very severe.

Streptomycin treatment was intentionally given alone, but after forty-eight hours the expected sterilization of the cerebrospinal fluid had not been obtained, although the dosage had been 0·12 g. six-hourly intramuscularly and 0·1 g. intrathecally daily. Sulphadiazine was therefore given in full doses in addition, but still without clinical or pathological response. Heparin, 5 mg., was also given daily intrathecally at this time, with no observable effect. On Nov. 10 and 11 additional streptomycin was given, into the ventricle and cisterna magna respectively, but without the fluid becoming sterilized. The patient's clinical condition remained grave, so intramuscular penicillin was started on Nov. 13 and streptomycin stopped on Nov. 14. The only effect of the streptomycin was that the resistance of the organism to the drug had multiplied fifty-fold in a week.

The illness was still out of control, and on Nov. 18 intrathecal penicillin was started and sulphamezathine added to the sulphadiazine. In accordance with the policy of Thomson et al. (1947), chloral was given before intrathecal penicillin on all occasions to reduce reaction. On Nov. 18, 50,000 units of crystalline penicillin, well diluted, were given. An hour later a severe reaction occurred, with collapse, vomiting, bradycardia, twitching, and coma; recovery was complete after five hours. To avoid further reactions subsequent dosage was more moderate and stepped up slowly.

By the use of penicillin and sulphonamides the condition was controlled; cerebrospinal fluid findings improved, and the boy's clinical response was good. On Nov. 24 the sulphonamides were stopped because of a rash, and a slight fever on the following day was also attributed to sulphonamide sensitivity.

The illness was punctuated by three relapses after this first period of control of the infection. Each time intrathecal penicillin was continued for a period after the last positive culture and then omitted if the clinical condition and appearance of the cerebrospinal fluid seemed to warrant it. The period of intrathecal treatment after the cerebrospinal fluid became clear was seven days before the first relapse, and this period was lengthened with each recrudescence to over two weeks in the last period.

FIRST RELAPSE. The first relapse occurred clinically on Nov. 28, immediately after intrathecal penicillin was withdrawn three days after completion of the sulphonamide course. Sulphamezathine was restarted and the dose of intramuscular penicillin was augmented, since in vitro tests had shown immense resistance to streptomycin, moderate resistance to sulphonamides, and relative sensitivity to penicillin. The patient was therefore given 600,000 units of penicillin per day in divided intramuscular doses and the intrathecal doses were stepped up to 25,000 units per day. The sulpha drug was discontinued on Dec. 3, but the clinical condition remained poor and the cerebrospinal fluid cell count rose slightly. On Dec. 13 sulphatriad was started. This is a mixture of the three sulphonamides found by Alexander (1947) to be most active, and it was given at first in the large doses of 7·5 g. per day. The fever continued, but after the cerebrospinal fluid had been sterile for eight days the intrathecal penicillin was stopped in case this was in fact the cause of the pyrexia.

SECOND RELAPSE. The second relapse occurred immediately when intrathecal penicillin was omitted on Dec. 15, and was clinical as well as bacteriological. (On the three previous days positive cultures had been obtained, but as they consisted of single colonies and demanded further identification the results were not available.) Control was re-established with intrathecal penicillin and large sulphonamide dosage, and this was maintained until Dec. 27, when intrathecal administration was reduced to alternate days without immediate ill effects. When the cerebrospinal fluid on Dec. 30 was found to be clear, intramuscular penicillin was stopped.

THIRD RELAPSE. The third relapse took place as soon as intrathecal penicillin was not given daily, and was seen bacteriologically on Dec. 30, 1947, and clinically on Jan. 2, 1948. The position was reviewed, and it seemed that no combination of the agents so far tried would be permanently effective. It appeared further that intrathecal penicillin with high doses of sulphonamide was the most effective treatment. Intramuscular penicillin seemed to be useless.

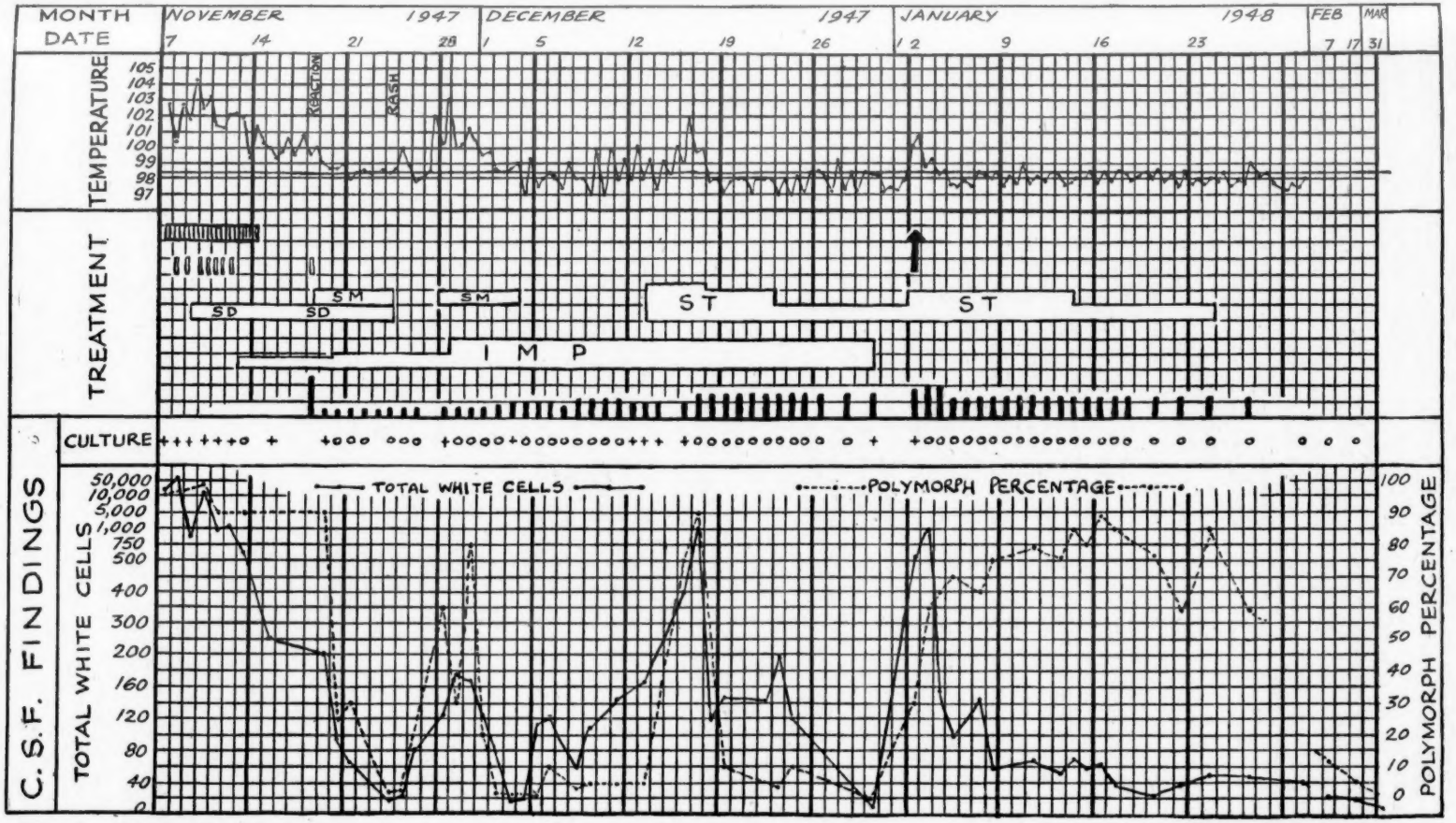
At this stage, therefore, haemophilus rabbit antiserum was given by slow intravenous drip, in a dosage of 50 mg. of antibody nitrogen. It must be mentioned here that in the week following the injection of the antibody no excess of it was demonstrable in the blood. The sulphatriad dosage was stepped up again to 6 g. per day, and daily intrathecal penicillin was resumed, although after the first three days the amount was less than had previously failed to produce permanent sterilization of the cerebrospinal fluid.

Prompt clinical response occurred, and the cerebrospinal fluid became, and remained, sterile. Improvement was maintained and the patient was discharged on Feb. 8, 1948. He weighed 23 lb., and seemed normal for his age. There were no neurological sequelae, and he appeared mentally normal.

## PATHOLOGICAL FINDINGS

Only the cell count and polymorph percentage are represented in the graph. The protein curve follows roughly the cell curve, with which the sugar and chloride curves vary inversely.

It will be seen that the percentage of polymorphs




▭ —Streptomycin treatment (intramuscular and intrathecal).

0 —5 mg. heparin intrathecally.

SM —Sulphamezathine.

SD —Sulphadiazine.

ST —Sulphatriad.

IMP —Intramuscular penicillin.

↓ —Intrathecal penicillin.

↑ —Rabbit antiserum.

1 vertical division represents:

Sulpha 3 g.

Intramuscular penicillin 300,000 units.

Intrathecal penicillin 20,000 units.

TOTAL DOSES

Streptomycin, intramuscular 3·24 g.
intrathecal 1·0 g.

Heparin 40 mg.

Sulphamezathine 45·5 g.

Sulphadiazine 43 g.

Sulphatriad 204 g.

Penicillin, intramuscular 23,000,000 units.
intrathecal 1,329,000 units.

Rabbit antiserum 50 mg. antibody nitrogen.

in the cerebrospinal fluid fell after the first period of infection, and although rising transiently with each relapse the rise was not maintained, the polymorphs being rapidly replaced by lymphocytes. It was not until the antiserum was given that a polymorph predominance, such as is usually seen in influenzal meningitis, was achieved and maintained. After the antiserum also, the total count, which between the relapses had fallen to a very low figure, remained at a higher level.

The initial sensitivity of the H. influenzae to streptomycin was 2 units per ml. on Fildes' medium by the cup method. By the tube method in Levinthal broth, however, its sensitivity was 20 units per ml. This latter method approximates far more to in vivo conditions than does the plate method, and in the present case at least appears to give a more reliable indication of the response to therapy. Cultures obtained on the fourth day of streptomycin treatment had become resistant to 1,000 units per ml. by plate and tube methods.

Streptomycin blood levels fell from 64 units one hour after to 8 units six hours after the intramuscular injections, while levels of 16 to 32 units per ml. of cerebrospinal fluid were regularly found twenty-four hours after intrathecal injection.

The penicillin sensitivity of the organism by both plate and tube methods was 1 unit per ml. Of all the sulphonamide drugs available, none inhibited growth at concentrations less than 25 mg. per 100 ml. Neither of these two sensitivities had changed in the last positive culture.

In spite of nearly 300 g. of sulpha drugs, at no time did the blood leucocyte count fall below 6,000 per c.mm., there was never a threat of agranulocytosis, and sulphonamide crystals were never seen in the urine.

## Comment

Streptomycin in this case was a total failure. It was foredoomed because the organism was naturally too resistant, apart from its resistance being enhanced by treatment. Natural streptomycin resistance seems to be rare in America, but in three out of five cases of influenzal meningitis seen this winter the organism isolated has had the same order of streptomycin resistance as that in the case under discussion.

The antiserum used was made and purified here by the methods of Alexander (1939) and Alexander and Heidelberger (1940). The reluctance to use it before other agents had been fully tried was in proportion to the time and labour necessary to stimulate adequate antibody production in rabbits. The failure to demonstrate excess antibody in the blood was probably due to the small dose given relative to the severity of the case as judged by Alexander's criteria, and this again was influenced by the amount of antiserum available. Alexander et al. (1942) mention the presence of antibody to H. influenzae in a case recovering without antiserum treatment. Zinnemann (1946) also refers to three cases which developed antibody, of which two recovered and one died. In seven cases successfully treated here without antiserum, in no instance was antibody to be found in the blood. We feel, therefore, that the failure to demonstrate it in the case presented here does not mean that the antiserum played no part. Indeed we feel that the response, both clinically and cytologically, following its administration can only be attributed to the antibody given. This change in the cerebrospinal fluid cells from lymphocytes to polymorphs has not to our knowledge been previously reported.

It is obviously undesirable to create more drug-fast strains of organisms than can be possibly avoided. It is clear, too, from a perusal of the literature as well as in our own experience, that strains of H. influenzae differ widely in their sensitivity to the various therapeutic agents available. Thus, the treatment of a given case should depend upon the sensitivities of the organism concerned. The determination of these sensitivities may take up to three days in the laboratory, during which time some form of treatment must be started. We feel that during this period adequate doses of a sulphonamide, preferably sulphadiazine, and intrathecal penicillin should be given. This therapy gives a reasonable chance of cure, and even in the present refractory case achieved a measure of control. A precise regimen of treatment can be evolved only when laboratory investigations are completed.

## Summary

A case of H. influenzae meningitis is presented in detail.

Treatment with streptomycin was a total failure, and the disease was only partly controlled by penicillin and sulphonamides. After three relapses the case was cured by the addition of H. influenzae rabbit antiserum to these drugs.

We are grateful to Dr. W. J. Pearson for permission to publish this case.

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# CONGENITAL ATRESIA OF POSTERIOR CHOANAE

BY

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Congenital atresia of posterior choanae is a moderately rare condition, and although Boyd (1945) has accounted for 230 cases in the literature, description of the symptoms presenting at birth are very scanty. Unilateral choanal obstruction is very much more common than the complete bilateral obstruction that was found in the present case. Richardson (1913) described a similar case in which relays of assistants maintained an airway by keeping the mouth of the child open, until at the end of a fortnight oral breathing was established.

## Case Notes

A full-term male child was noticed at birth to have a fluttery type of breathing and was immediately laryngoscoped; mucus was removed from the larynx, which itself appeared quite normal. The respirations did not become regular and when the child was seen a few hours later the mouth was open and there were periods of apnoea followed by a few very rapid gasping breaths; the breathing appeared to be almost entirely abdominal, the diaphragm seeming to go into spasm and then to cause the fluttering movements of the abdomen. There was no obvious intercostal recession, the chest remaining inflated; on auscultation the air entry was poor, but there were no added sounds.

A radiograph showed no abnormality in lungs or heart.

At first it was thought that the condition was due to partial bronchial obstruction by mucus, but the child failed to improve, and had great difficulty in taking feeds, failing entirely from the breast and almost entirely from the bottle. On the third day of life attempts were unsuccessfully made to pass first a soft rubber and then a silver Eustachian catheter through the nose. A diagnosis of bilateral imperforate posterior choanae was made; about this time a thick mucoid nasal discharge appeared and rapidly became more profuse.

On the fifth day of life it was decided that a surgical attempt should be made to establish a nasal airway. A few drops of 1 per cent. amethocaine solution were instilled into each nostril and allowed to remain for ten minutes, with the baby lying on its back. The mouth was so small that digital examination of the nasopharynx was impossible, but exploration with a bent probe revealed the existence of a post-nasal space. Using an antrum burr the posterior choanal obstruction was broken down first on one side and then on the other. The choanal partitions were much thicker than was expected and considerable force had to be used in order to penetrate them with the burr. Care was taken not to penetrate the soft palate—a mishap which can easily occur with such a tiny patient—by placing a palpating finger against the buccal surface of the palate in order to determine the position of the advancing burr head. The smallness of the nostrils precluded the use of any kind of punch forceps, and it was not possible to remove with precision any part of the posterior margin of the nasal septum. Nevertheless posterior choanal openings sufficiently large to admit the passage of a full-sized frontal sinus bougie were established.

The operation was accompanied by surprisingly little shock, and the child was brought out of the theatre breathing normally, with the mouth closed. After a few hours the mucoid nasal discharge caused a recurrence of the symptoms and it became necessary frequently to suck the nose clear. The child had to be spoon-fed, until eventually the discharge decreased and it became possible to feed him from the breast.

After operation he was treated with nasal drops, at first alkaline, and then ephedrine 0·5 per cent. in normal saline; frontal sinus bougies were passed, at first daily, and then at longer intervals. A peculiar feature of this period was persistence of a very rapid respiratory rate and the occurrence of 'grey' turns during feeding.

He was eventually discharged one month after birth, in good condition and weighing 8 lb., his birth weight having been 7½ lb.

He was readmitted fourteen days later with an acute upper respiratory infection and nasal obstruction due to mucopurulent discharge, and he died in forty-eight hours. Post-mortem examination showed that a reasonable airway had been obtained through the posterior choanae and that the post-nasal space was not constricted, although blocked by thick pus. The heart was moderately enlarged, the ductus arteriosus was widely patent, and there was an abrupt narrowing of the aorta between the left subclavian artery and the ductus, causing a

coarctation of the foetal type. The remaining findings did not contribute to the condition.

## Summary

An account is given of a case of complete bilateral posterior choanal obstruction in an infant, dramatically but temporarily relieved by operation; owing to the occurrence of a mucoid nasal discharge the symptoms reappeared for a while. Death from an upper respiratory infection occurred at the age of six weeks.

## References

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# REVIEWS

**Congenital Malformations of the Heart.** By HELEN B. TAUSSIG, M.D., Associate Professor of Pediatrics, Johns Hopkins University School of Medicine. 1947. New York: The Commonwealth Fund (London: Oxford University Press). Pp.618. (Price $10.00.)

The author's name is already well known as Dr. Blalock's collaborator in the design of the Taussig-Blalock operation. This book contains amongst much else the detailed studies of the congenital cardiac malformation for the relief of which this operation has been undertaken, and emphasizes the particular radiological techniques which make accurate diagnosis possible during life. The author makes it clear that it is a monograph written from personal experience, and she has therefore limited herself to a detailed consideration of those methods which she has actually used. Whilst the book is exceptionally comprehensive, the clinical study of the heart by catheterization and the use of radio-opaque substances has developed so rapidly since it was written that it must be regarded as saying the penultimate rather than the last word on the subject. It is profusely illustrated with line and colour diagrams, and beautifully produced.

**Elêments de Puêriculture.** By B. WEILL-HALLE, Directeur honoraire de l'Ecole de Puêriculture de la Faculté de Mêdecine de Paris. 1947. Paris: L'Expansion Scientifique Française. Pp. 260. (Price 450 French *fr.*)

This little book, dealing with the physical and mental development of the child, is 'guide aux mamans' rather than a contribution to the scientific literature. Written during the occupation, it bears unavoidable signs of detachment from the recent advances which have been made, particularly in the U.S.A., in the study of child development. It contains, however, a liberal sprinkling of the salt of wise counsel and a peppering of outworn shibboleths.

**Malaria im Kindesalter.** By Prof. Dr. med. ALBERT ECKSTEIN. Professor of Children's Diseases, Ankara. 1946. Basel: S. Karger. Pp. 119. (Price 14 Swiss *fr.*)

This is one of the best monographs on malaria in childhood that has been produced. The author deals in detail with prophylaxis, treatment, the clinical picture, and complications. The sections on congenital malaria and 'malarial dystrophy' are of particular interest.

**Breast Feeding.** By F. CHARLOTTE NAISH, B.A., M.B., B.Ch. (Cantab.). 1948. London: Geoffrey Cumberlege, Oxford University Press. Pp. 151. (Price 10*s.* 6*d.*)

It is many years since a Regius Professor of Physic disallowed the thesis 'That Breast Milk is the Best Food for Babies' on the grounds that it was self-evident. One now hears of clinics where a healthy mother who is anxious to breast-feed her baby has to struggle against medical as well as family opposition. Dr. Naish's book is therefore all the more welcome, and one feels the judges were wise in awarding this the Sir Charles Hastings Clinical Essay Prize for 'the promotion of systematic observation, research and record in general practice'. The author writes from personal experience as a mother in addition to observation and management of others, and the reader inevitably gains the impression that she knows what she is talking about. The reviewer has often wondered how nursing mothers so patiently tolerate the pontifications of male, or unmarried female, paediatricians, and this 'guide to the natural feeding of infants' should carry conviction in a way that more scientific writings may fail to do. On the other hand, the author might perhaps have been a little more critical when she recommends such unnatural feeding as thyroid for torpor in the first week of life; the reader might reasonably expect some critical assessment of the evidence of its value. Similarly, when she emphasizes that underfeeding is a more important cause of difficulty than overfeeding (in which she is no doubt right), it is salutary to remember that a previous generation of students was being taught the exact reverse by paediatricians also armed with test-weighing machines. Here some exact figures might well be included to drive home the point. Apart from such very minor criticisms, however, this essay can be warmly recommended and endorsed; the chapter on 'The Mind of the Mother' is properly selected for special mention by Professor Moncrieff in his breezy foreword.